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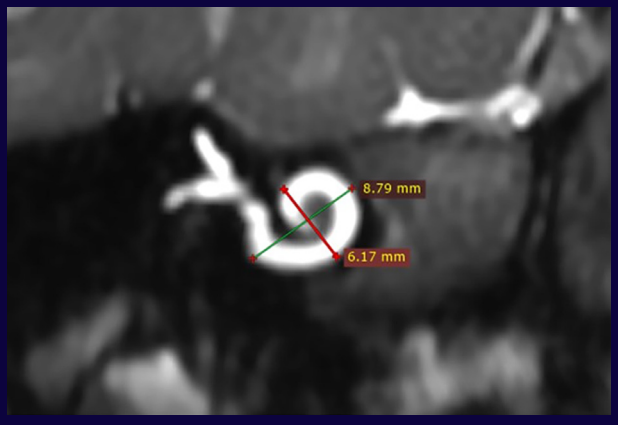

Cochlear Duct Length: Rethinking Its Role in Auditory Outcomes
Page: 124-130

Original Investigations

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Contents

Cochlear Duct Length: Rethinking Its Role in Auditory Outcomes

Original Investigation

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Abstract

Objective: To assess the relation between cochlear duct length (CDL) and audiological outcome after cochlear implant surgery in prelingually deafened children.

Methods: In a prospective cohort study, 36 prelingually deaf children underwent cochlear implantation at All India Institute of Medical Sciences, Jodhpur. Preoperative high-resolution computed tomography (HRCT) and high-resolution T2 weighted sequences magnetic resonance imaging (MRI) of temporal bones were used to calculate CDL. Patients were followed up for 12 months postoperatively with visits every three months for audiological scoring (infant-toddler meaningful auditory integration scale and revised central auditory processing scores).

Results: Thirty-six candidates were included in the study. The mean CDL, as measured on temporal bone HRCT, was 32.72±1.278 mm, and, with MRI, was 33.4689±1.31. This study is suggestive of widely dispersed data (coefficient of variance <0.5), and hence, the hypothesis of "implantation in CDL close to 31.5 mm will give the best improvement in functional outcome scores" cannot be generalized. The improvement in functional outcome scores is likely attributable to other causes/multifactorial causation.

Conclusion: We found no relationship between CDL and audiological outcomes post-cochlear implantation in prelingually deaf children. Further research with larger sample sizes, prospective multicenter designs and extended follow-up periods is warranted to strengthen evidence in this area.

Keywords: Hearing loss, cochlear implantation, cochlear duct, radiology, audiology, patient outcome assessment, pediatric otorhinolaryngology

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Introduction

The anatomy of the cochlea is the most significant factor for successful cochlear implantation. Cochlear anatomy varies among humans, so measuring the cochlear duct length (CDL) forms the basis for achieving better cochlear implant results. CDL is defined as the length of the scale media, measured from the middle of the round window to the helicotrema (1). Precise knowledge of CDL is crucial if accurate placement of the intracochlear electrode array is required while preserving residual hearing. Additionally, with the advancements in cochlear implants,

variable lengths of electrodes are now available in the market for implantation. Reports of incomplete insertion of longer electrodes highlight the variability in the length of the cochlear duct as a significant factor in the depth of insertion (2). Therefore, preoperative estimation of CDL and precise insertion of the electrode array can significantly contribute to the success of cochlear implantation. The measurement of CDL has been conducted radiographically (3). At our center, it is routine for all patients with congenital hearing loss to undergo high-resolution computed tomography (HRCT) of the temporal bone as part of the cochlear implantation workup. Using software and mathematical formulas, we can calculate the CDL. Our study focuses on the Asian race, specifically the North Indian race, characterized by smaller skulls.

There are two main perspectives on cochlear implantation. One believes the best outcomes occur when residual hearing is preserved, even in patients with profound hearing loss (4). Some surgeons prefer inserting an electrode up to 80% of the cochlear duct to avoid disturbing apical hair cells (electroacoustic stimulation) (5), thus preserving residual hearing. For this reason, some institutions use a two-turn length measurement of the cochlea to err on the side of caution. The other perspective argues for deeper insertion to stimulate frequencies along the cochlea's spiral ganglion. Newer, more flexible electrodes taper towards the apex (direct apical hair cell stimulation), allowing full insertion and better stimulation of lower speech frequencies (6).

Few studies correlate auditory outcomes with CDL. We use Medel's 31.5 mm electrode, which claims atraumatic insertion and optimal positioning in the apical turn. We hypothesize that electrodes around 31.5 mm, inserted atraumatically, will stimulate a more comprehensive frequency range, leading to better speech outcomes.

Methods

Study Design

Prospective cohort study.

Study Setting

The department of otorhinolaryngology and the department of intervention and diagnostic radiology collaborated at the All India Institute of Medical Sciences (AIIMS), Jodhpur, and Rajasthan (India).

Study Duration

Two years and three months (17th Nov 2020-28th Feb 2023). Patients aged less than 36 months were enrolled in the study. Approval All India Institue of Medical Sciences, Jodhpur Institutional Ethics Committe (IEC), AIIMS (IEC reg. no.: AIIMS/IEC/2020/3163, date: 23/09/2020), and registration was done with Clinical Trial Registry-India (CTRI Registration No.: CTRI/2020/11/029149 obtained on: 17/11/2020). Informed and written consent in a language the parents could understand was obtained from them before they participated in the study.

Preoperative Evaluation

All candidates underwent preoperative evaluation, including audiological evaluation [brainstem evoked response audiometry (BERA), auditory steady state response (ASSR), oto-acoustic emission, tympanometry, aided audiogram], radiology (temporal bone HRCT, inner ear MRI), TORCH profile, and assessments by various departments like pediatrics for ruling out the syndromic association, cardiology for ruling out structural heart abnormality and Long QTc syndrome, ophthalmology, and psychological evaluation for intelligence quotient and behavioral assessment, developmental quotient and social quotient.

Measurement of CDL on temporal bone HRCT and MRI

To get the full basal turn, the cochlea was organized in the double oblique coronal plane (Figure 1, green line). Heavily T2 weighted cumulative uncertainty-based evaluation sequences were used for calculating CDL in MRI.

CDL=4.16A-3.98 (1,7,8)

CDL refers to CDL, and A is the largest measured length from the round window to the cochlea's lateral wall going through the modiolus.

In the study, individuals with profound hearing loss, as indicated by ASSR and the absence of waves up to 90 dB in BERA, were considered. Two independent radiologists calculated the CDL in both computed tomography (CT) and MRI, and the average value was taken.

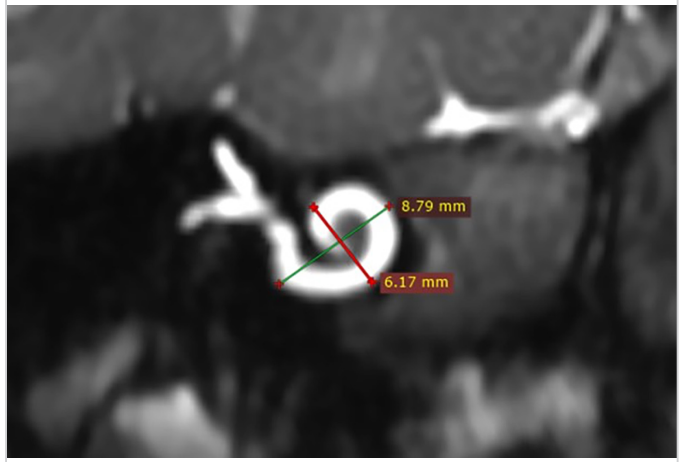

Figure 1. Double oblique coronal reformatted image of cochlea in MRI (heavily T2-weighted CUBE sequence)
MRI: Magnetic resonance imaging, CUBE: Conventional unilateral brain exploration

Exclusion Criteria

Children with a CDL of less than 31.5 mm and an age of more than three years were excluded from the study. Additionally, individuals with anomalous cochlea, low IQ, syndromic association, or genetic disorders were also excluded.

All patients had both ears stimulated with hearing aids for three months preoperatively. Subsequently, all patients underwent unilateral right-side implantation.

Patients with residual hearing or those who demonstrated improved aided audiometry after a minimum use of external hearing aids for three months were identified during preoperative evaluations.

Refined Study Approach and Ethical Considerations

Unlike the studies in literature that have adopted the predominant linear relationship focus between CDL and speech outcomes, our study has adopted a nuanced approach. We incorporated the theory of complete tonotopic stimulation by selecting an electrode array closely aligned with CDL.

The following assumptions guide our methodology:

Ethical Exclusion Criteria

Using an electrode array in a relatively smaller CDL is hypothesized to result in complications like kinking, bending, trauma, or displacement.

Recognizing the ethical implications, patients with CDL smaller than the electrode length were ethically excluded from the study.

Inserting a 31.5 mm electrode into a smaller CDL is considered ethically inappropriate and contradicts the concept of residual hearing preservation.

Surgical Technique

All surgeries were performed by a senior neuro-otologist with extensive experience in cochlear implantation surgery using the veria technique (9,10) (Figure 2). Our study used Med-El Sonata ti100 standard (Electrode volume-13 μL) in all 36 candidates.

Smooth Insertion Process

Meticulous exclusion of ineligible patients facilitated a smooth insertion of the electrode array in all subjects (11). Intraoperatively, resistance-free insertion was achieved until the level of marking (blue indicator) on the electrode. Patients experiencing resistance or not undergoing full-length insertion (not reaching the mark) were excluded from the study for further radiological evaluation to assess the position, over-insertion, kinking, and bending at the apex.

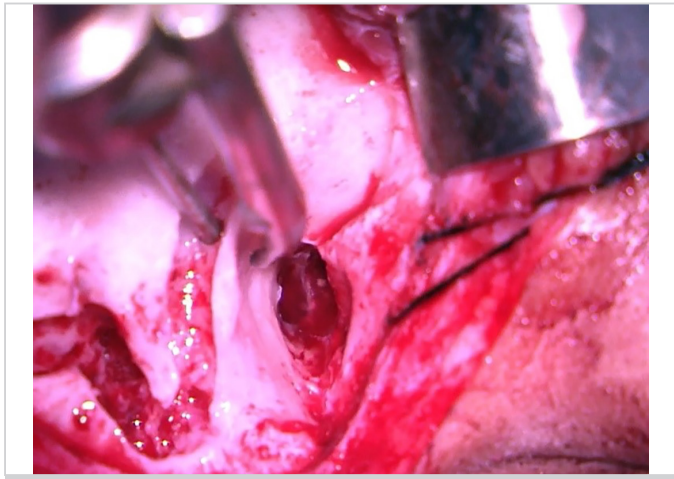

Figure 2. Veria technique: drilling of a tunnel parallel (1.4 mm) to posterior canal wall using Trifon's perforator with guard for electrode insertion (11 o'clock) on right ear

Intraoperative neural response telemetry (NRT) assessments were done in patients, and those experiencing difficulties or complications were also excluded from the study. Amplitude in the electrodes' apical, middle, and basal turns on electrically evoked compound action potential (ECAP) stimulation was recorded. To avoid unnecessary radiation exposure, especially considering our pediatric age group, the position of the electrodes were confirmed using postoperative X-ray instead of routine postoperative CT scanning. The use of radiation was approached cautiously in pediatric cases.

Follow-up

Candidates who underwent cochlear implantation participated in a preoperative assessment using the revised categories of auditory performance score (Revised CAP) and infant toddler meaningful auditory integration scale (IT-MAIS) one week before surgery (12-14). Subsequently, candidates were contacted every three months post-switch-on, with all patients completing a one-year follow-up post-switch-on (15).

Statistical Analysis

All data collected was tabulated in an Excel spreadsheet and was analyzed using the Statistical Package for Social Sciences (SPSS). International Business Machines (IBM) Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp. The results of the categorical measurements were presented in numbers or ratios. Results of quantitative variables were presented as median (95% confidence interval) or mean±SD, Pearson's correlation coefficient, One-Way Analysis of Variance test. The level of significance was taken as 5% with a p-value <0.05 being considered significant.

Results

The final assessment included 36 implanted children after applying all exclusion criteria, forming the basis for calculating the results. The study population includes children who are less than three years of age, of whom 90.78% were aged between 28 and 36 months (Figure 3).

The mean CDL measured on temporal bone HRCT was 32.72±1.278 mm and on MRI was 33.4689±1.31 mm.

The graph shows a plot between CDL and improvement in CAP score from preoperative period to postoperative 12th month (Figure 4). The downward slope of regression equation is suggestive of relatively more improvement in the CAP score in the length of the lower cochlear duct compared to the length of the higher cochlear duct. This is a widely dispersed scatter plot (R^2-0.005) which signifies that the improvement in the CAP score was not strongly correlative with CDL change, and multifactorial cause can be attributed.

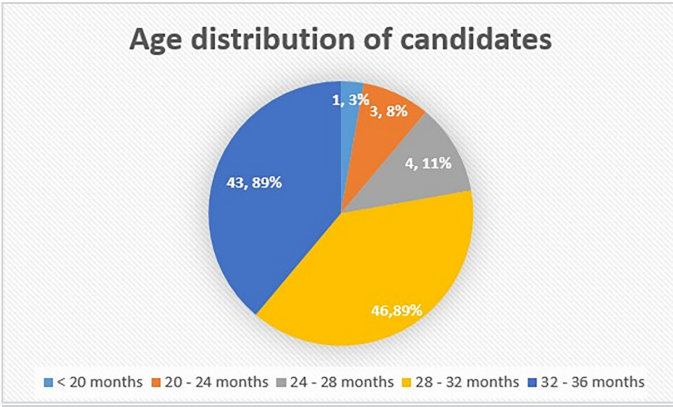

Figure 3. Pie diagram showing age distribution of the cochlear implanted population

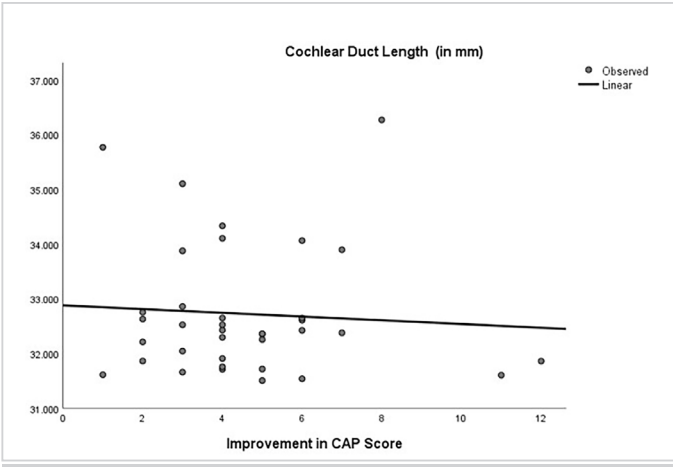

Figure 4. The graph shows a plot between cochlear duct length and improvement in categories of auditory performance score from preoperative period to 12 months postoperatively

The graph shows a plot between and improvement in IT-MAIS score from preoperative period to postoperative 12th month (Figure 5). The downward slope of regression equation is suggestive of relatively more improvement in the IT-MAIS score in the length of the lower cochlear duct compared to the length of the higher cochlear duct (r=-0.122). The highest improvement in the IT-MAIS score was found with CDL of 32.281 (average).

The graph shows good homoscedasticity for the least square method regression equation.

The scatter plot in the above analysis is suggestive of widely dispersed data (coefficient of variance <0.5) (Figure 6) and hence the hypothesis of "implantation in CDL close to 31.5 mm will give best improvement in functional outcome scores" cannot be generalized. The improvement in functional outcome scores is likely attributable to other causes/multifactorial causation.

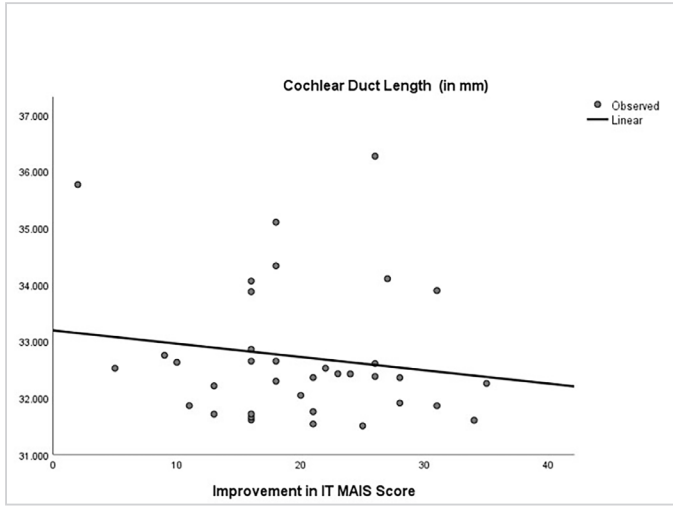

Figure 5. The graph shows a plot between cochlear duct length and Improvement in infant toddler meaningful auditory integration scale (IT-MAIS) score from preoperative period to 12 months postoperatively

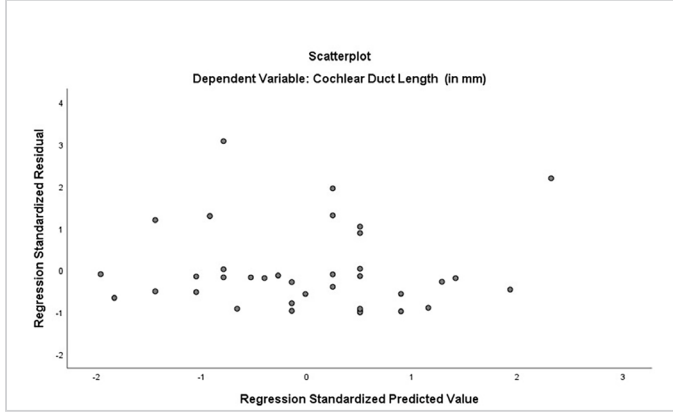

Figure 6. Scatter plot in above analysis is suggestive of widely dispersed data (coefficient of variance <0.5)

Discussion

Cochlear implants have existed for over 40 years, with nearly 20 years of presence in India. As we reflect on this established technology, it is imperative to explore futuristic aspects tailored to individual patients based on the unique anatomy of the cochlea. This involves incorporating current theories of residual hearing preservation and leveraging the maximum benefit of tonotropicity (16).

In the current market, various cochlear implant models claim effectiveness in cases with anomalies and lesser CDLs. These models differ in electrode arrays and thickness and employ multiple engineering techniques to provide maximum acoustic stimulation, including targeting apical low-frequency hair cells and achieving improved insertional depth. While the cochlear duct has been widely discussed as a parameter, there still needs to be clear evidence of the tonotopic distribution within a cochlea, which may vary among individuals based on factors such as ethnicity and race.

In light of existing evidence, we hypothesize that an electrode array inserted atraumatically, with a length similar to the CDL, can cover the entire tonotopic region. Although there are limited studies linking CDL to long-term postoperative auditory outcomes, there is a notable absence of research utilizing the same electrode in prelingual age-stratified data.

A study by Jain et al. (17) in 2020 examined the relationship between postoperative audiological results and cochlear nerve cross-section as determined by MRI, finding no association.

Kuthubutheen et al. (18) suggested no correlation between CDL and audiological outcomes in post-lingual patients using Med-El Flexsoft™ (Flex 31) and Flex28™ (Flex 28) implants.

Johnston et al. (19) study indicated that preoperative CDL measurement could predict full electrode insertion but found no correlation with audiological outcomes.

Our study hypothesized that smaller CDL could result in incomplete implant electrode insertion, while longer lengths could leave unstimulated areas near the helicotrema, particularly affecting lower frequencies. Given the tonotopic division of the cochlea based on frequency, it is expected that complete stimulation across all cochlear areas would yield better audiological outcomes. In scenarios with incomplete cochlear coverage, poorer auditory results are anticipated (20).

Despite existing studies, there is still a gap in understanding the relationship between cochlear parameters and audiological outcomes, especially in prelingually deaf children. This study aims to contribute valuable insights by investigating the impact of CDL on cochlear implantation outcomes in this specific population, thereby aiming for the need for a patient-specific customized electrode array for better speech outcome.

In contrast to the predominant focus on establishing a linear relationship between CDL and speech outcomes in existing studies, our approach seeks to address this gap by embracing the theory of complete tonotopic stimulation. We emphasize selecting an electrode array that closely aligns with the CDL.

In our study, all 36 cochlear implant recipients received a unilateral Med-El Sonata Ti100 STANDARD cochlear implant. The mean CDL, as measured on temporal bone HRCT, was 32.72±1.278 mm, and on MRI was 33.4689±1.31 mm. We used the same formula, and the two mean values are comparable; however, we used the HRCT values for correlation for statistical purposes because we found existing studies that were calculated using HRCT with the same demographic data (Western Rajasthan, India) for better reliability.

Based on prior studies, it has been determined that there is an inverse relationship between the age of cochlear implantation and the improvement observed in IT-MAIS and CAP scores. This implies that an infant undergoing cochlear implantation at one year could achieve the desired IT-MAIS and CAP scores within three months. Conversely, achieving similar results could take up to twelve months for those who receive implants at the age of three years.

We conducted analyses of CAP and IT-MAIS scores at three months, six months, and 12 months post-implantation, focusing exclusively on children aged under 36 months. Thus, the selection criterion aimed to minimize variation in CAP and IT-MAIS scores among implant recipients under 36 months. Notably, our findings revealed that children implanted between three to five years of age required additional years of auditory-verbal therapy (AVT) to attain CAP and IT-MAIS scores comparable to those achieved by younger recipients within one-year post-implantation, hence excluding the age group of more than three years. Postoperative AVT was administered to all patients, with cochlear measurements and outcome evaluations conducted by impartial observers to minimize bias.

We used lateral wall-hugging electrodes. Perimodiolar hugging electrodes can have an increased risk of scalar shift. Liebscher et al. (21) did not find measurable differences in the word recognition score (WRS). In contrast, Aschendorff et al. (22) reported a detrimental effect of dislocation of up to 10 percentage points (pp) for the WRS of patients with scalar dislocations as well as perimodiolar electrodes are shorter and cannot stimulate lesser frequency hair cells located at the apical turn.

Interestingly, bilaterally implanted infants demonstrated the potential to achieve near-normal CAP scores shortly

after surgery, underscoring the efficacy of early intervention. Consequently, we adopted a one-year time frame for assessing children under three years of age, presuming minimal impact of neuroplasticity during this period.

Our study standardized the electrode choice to the 31.5 mm Med-El standard electrode for all patients, excluding those with CDL less than 31.5 mm. We emphasized gentle, smooth insertion techniques to minimize complications regardless of electrode choice. Tactile feedback during insertion was crucial, with any perception of resistance prompting reassessment to prevent electrode malposition. Complete insertion up to the marker without resistance was ensured, with each cochleostomy packed to enhance scar tissue formation and minimize complications.

Intraoperative NRT assessments were normal for all patients. All the patients showed desirable amplitude in the apical turn, middle and basal turn of the electrodes on ECAP stimulation, indirectly reflecting stimulation of active hair cells of all the regions of the cochlea after the insertion of electrodes (23). In one study (24), different electrodes were used to assess the effect of speech outcome and the results were different with different electrodes. Hence, we used the same electrode in all patients to reduce the confounder.

Postoperative radiology was conducted selectively, with MRI preferred over CT to avoid unnecessary radiation exposure. Due to resource constraints and logistical challenges, intraoperative assessment was deemed sufficient, supported by literature demonstrating its reliability.

As per the literature, the choice between cochleostomy and round window insertion did not yield significant differences in speech outcomes at the 12-month postoperative mark (25). Although findings suggesting improved outcomes with shorter CDL indirectly imply comprehensive stimulation across tonotopic areas in patients lacking residual hearing or experiencing hearing enhancement after three months of acoustic stimulation, this raises questions regarding preserving residual hearing by avoiding full insertion. However, the robustness of our study in substantiating this hypothesis is limited due to the absence of a linear relationship observed in the study. Hence, reliance solely on CDL may not always hold, given the multifactorial nature influencing speech outcomes despite extensive exclusion criteria. Our study poses a significant query regarding CDL, which is particularly noteworthy as many implant companies prioritize this metric. Our study revealed no statistically significant correlation between CDL and audiological outcomes, even at 12 months postoperatively, as confirmed by scatter plot analysis. Consequently, including additional results at three and six months is deemed unnecessary.

Conclusion

In conclusion, our study found no significant relationship between CDL and audiological outcomes following cochlear implantation in prelingually deaf children, even after applying multiple exclusion criteria at various levels (demographic, clinical assessment, radiological, surgical technique, and NRT to minimize the potential confounders. Future research with larger sample sizes, matching, prospective multicenter designs, and longer follow-up periods is needed to provide more substantial evidence in this area.

Ethics

Ethics Committee Approval: Approval to conduct this study was taken from the Institution Ethics Committee (IEC), AIIMS (IEC Reg. No.: AIIMS/IEC/2020/3163, date: 23/09/2020).

Informed Consent: Informed and written consent in a language the parents could understand was obtained from them before they participated in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: P.A., P.S.K., A.G., Concept: S.T., A.G., Design: V.S., D.K., K.S., A.G., Data Collection and/or Processing: P.A., Analysis and/or Interpretation: V.M., S.T., Literature Search: V.S., P.S.K., Writing: P.A., V.M.

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

Financial Disclosure: The author(s) declare that no financial interests or relationships that could be perceived as influencing the research presented in this article.

Main Points

- Theoretically, cochlear duct length (CDL) is an important tool for predicting the accuracy of electrode placement.
- Limited clinical outcomes of CDL measurements are present in the existing literature.
- The infant toddler meaningful auditory integration scale and modified compound action potential (CAP) score are easy and parent-friendly tools to assess performance in post-implant children.
- While preoperative CDL measurement is helpful for precise selection of an electrode with a matching length, there is no substantial improvement in speech outcomes directly correlated with CDL.
- Speech outcome shows no correlation even after matching the age, race, intelligence quotient, device selection, operating surgeon, and operating conditions. Therefore, overemphasizing CDL should be minimized.

References

1. Grover M, Sharma S, Singh SN, Kataria T, Lakhawat RS, Sharma MP. Measuring cochlear duct length in Asian population: worth giving a thought! Eur Arch Otorhinolaryngol. 2018; 275: 725-8. [Crossref]
2. Spiegel JL, Polterauer D, Hempel JM, Canis M, Spiro JE, Müller J. Variation of the cochlear anatomy and cochlea duct length: analysis with a new tablet-based software. Eur Arch Otorhinolaryngol. 2022; 279: 1851-61. [Crossref]
3. Singh A, Kumar R, Manchanda S, Bhalla AS, Sagar P, Irugu DVK. Radiographic measurement of cochlear duct length in an Indian cadaveric population - importance of custom fit cochlear implant electrodes. Int Arch Otorhinolaryngol. 2020; 24: e492-5. [Crossref]
4. Lin CC, Chiu T, Chiou HP, Chang CM, Hsu CJ, Wu HP. Residual hearing preservation for cochlear implantation surgery. Tzu Chi Med J. 2021; 33: 359-64. [Crossref]
5. Turner CW, Gantz BJ, Karsten S, Fowler J, Reiss LA. Impact of hair cell preservation in cochlear implantation: combined electric and acoustic hearing. Otol Neurotol. 2010; 31: 1227-32. [Crossref]
6. Hochmair I, Hochmair E, Nopp P, Waller M, Jolly C. Deep electrode insertion and sound coding in cochlear implants. Hear Res. 2015; 322: 14-23. [Crossref]
7. Mistrík P, Jolly C, Sieber D, Hochmair I. Challenging aspects of contemporary cochlear implant electrode array design. World J Otorhinolaryngol Head Neck Surg. 2017; 3: 192-9. [Crossref] DOI: 10.1016/j.wjorl.2017.12.007
8. Thong JF, Low D, Tham A, Liew C, Tan TY, Yuen HW. Cochlear duct length–one size fits all? Am J Otolaryngol. 2017; 38: 218-21. [Crossref]
9. Hans JM, Prasad R. Cochlear implant surgery by the veria technique: how and why? Experience from 1400 cases. Indian J Otolaryngol Head Neck Surg. 2015; 67: 107-9. [Crossref]
10. Singhal P, Nagaraj S, Verma N, Goyal A, Keshri A, Kapila RK, et al. Modified veria technique for cochlear implantation by postaural approach. Indian J Otolaryngol Head Neck Surg. 2020; 72: 370-4. [Crossref]
11. Friedland DR, Runge-Samuelson C. Soft cochlear implantation: rationale for the surgical approach. Trends Amplif. 2009; 13: 124-38. [Crossref]
12. Zhou H, Chen Z, Shi H, Wu Y, Yin S. Categories of auditory performance and speech intelligibility ratings of early-implanted children without speech training. PLoS One. 2013; 8: 53852. [Crossref]
13. Sharma S, Solanki B, Solanki Y, Kaurani Y. Cochlear implants: evaluation of effects of various parameters on outcomes in pediatric patients at a tertiary care centre for unilateral ear implantation. Indian J Otolaryngol Head Neck Surg. 2022; 74: 360-7. [Crossref]
14. Zhong Y, Xu T, Dong R, Lyu J, Liu B, Chen X. The analysis of reliability and validity of the IT-MAIS, MAIS and MUSS. Int J Pediatr Otorhinolaryngol. 2017; 96: 106-10. [Crossref]
15. Ben-Itzhak D, Greenstein T, Kishon-Rabin L. Parent report of the development of auditory skills in infants and toddlers who use hearing aids. Ear Hear. 2014; 35: 262-71. [Crossref]
16. Manley GA. Travelling waves and tonotopicity in the inner ear: a historical and comparative perspective. A Neuroethol Sens Neural Behav Physiol. 2018; 204: 773-81. [Crossref]
17. Jain S, Sharma V, Patro SK, Khera P, Yadav T, Tiwari S, et al. Correlation of cochlear nerve cross-sectional area and auditory performance after cochlear implantation in prelingual children with bilateral profound hearing loss. Int J Pediatr Otorhinolaryngol. 2020; 137: 110173. [Crossref]
18. Kuthubutheen J, Grewal A, Symons S, Nedzelski J, Shipp D, Lin V, et al. The effect of cochlear size on cochlear implantation outcomes. BioMed Res Int. 2019; 2019: 1-8. [Crossref]
19. Johnston JDA, Scoffings D, Chung M, Baguley D, Donnelly NP, Axon PR, et al. Computed tomography estimation of cochlear duct length can predict full insertion in cochlear implantation. Otol Neurotol. 2016; 37: 223-8. [Crossref]
20. Doubi A, Almuhawas F, Alzhrani F, Doubi M, Aljutaili H, Hagr A. The effect of cochlear coverage on auditory and speech performance in cochlear implant patients. Otol Neurotol. 2019; 40: 602-7. [Crossref]
21. Liebscher T, Mewes A, Hoppe U, Hornung J, Brademann G, Hey M. Electrode translocations in perimodiolar cochlear implant electrodes: audiological and electrophysiological outcome. Z Med Phys. 2021; 31: 265-75. [Crossref]
22. Aschendorff A, Kromeier J, Klenzner T, Laszig R. Quality control after insertion of the nucleus contour and contour advance electrode in adults. Ear Hear. 2007; 28: 75-9S. [Crossref]
23. Brill S, Müller J, Hagen R, Möltner A, Brockmeier SJ, Stark T, et al. Site of cochlear stimulation and its effect on electrically evoked compound action potentials using the MED-EL standard electrode array. Biomed Eng OnLine. 2009; 8: 40. [Crossref]
24. Büchner A, Illg A, Majdani O, Lenarz T. Investigation of the effect of cochlear implant electrode length on speech comprehension in quiet and noise compared with the results with users of electro-acoustic-stimulation, a retrospective analysis. PLoS One. 2017; 12: e0174900. [Crossref]
25. Rajput M, Nilakantan A. Functional outcomes in cochleostomy and round window insertion technique: difference or no difference? Indian J Otolaryngol Head Neck Surg. 2019; 71: 1615-20. [Crossref]

Tinnitus: Does it Lead to Impairments in Metacognitive Functions and the Theory of Mind Skills?

Original Investigation

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Abstract

Objective: This study aimed to investigate theory of mind skills and metacognitive functions in patients with tinnitus compared to healthy controls

Methods: This prospective study included patients diagnosed with tinnitus at our otolaryngology and Head and Neck Surgery clinic and healthy controls matching their demographic characteristics. Patients diagnosed with tinnitus at our otolaryngology and head and neck surgery clinic, along with healthy controls matched for demographic characteristics, were included in the study. All participants completed the Reading the Mind in the Eyes Test (RMET), the metacognition questionnaire (MCQ-30), the Beck Depression Inventory (BDI), and the Tinnitus Handicap Inventory (THI). The relationship between the scales applied to the patient group regarding tinnitus was evaluated using Spearman's and Pearson's correlation tests.

Results: A total of 90 individuals diagnosed with tinnitus and 70 healthy controls participated in the study. There was no statistically significant difference in BDI scores between the groups (p>0.05). However, in the MCQ-30, the cognitive awareness subscale and the total score were significantly higher in the tinnitus group (p=0.003 and p=0.041, respectively). Additionally, RMET performance was lower in tinnitus patients compared to healthy controls (p=0.002). Certain subscales of the MCQ-30 showed a moderate positive correlation with THI.

Conclusion: Based on these findings, we suggest that evaluating tinnitus patients from a psychiatric perspective, providing psychosocial support, and assisting them in improving their communication skills could be beneficial.

Keywords: Tinnitus, cognition, emotions, cognition disorders, psychological distress, depression, anxiety

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Introduction

The Theory of Mind (ToM) is defined as the ability to understand and perceive one's own and others' mental states (1). Another definition states that it refers to the ability to predict and understand the unobservable mental states of individuals, such as desires, emotions, beliefs, intentions, and motivations (2). ToM is a developmental skill that starts in early childhood and continues to develop and progress into adolescence, young adulthood, and adulthood (1,3). With advancing age, the development and progression of ToM skills enable individuals to have a better understanding of new, unexpected, and ambiguous situations and emotions (3). Recent research has shown that ToM skills have two different dimensions: emotional and cognitive. Emotional ToM skills involve the ability to make inferences about how others feel, while cognitive ToM skills involve the ability to reason about how others think (4). Given these descriptions, ToM skills are a complex field of study that involves various disciplines such as developmental psychology, education, psychiatry, and neurology (1-3).

Metacognition is defined in the field as "thinking about thinking" (5). Although this definition is limited to the person's own mental state and her/his own thoughts, it actually includes the thoughts of others (6). The closely related concept of the ToM, examined under the same title, is the ability to understand other people's feelings, thoughts, and intentions. It was first put forward in 1978 by Premack and Woodruff (2) in studies conducted with chimpanzees (1,2). It was then used in studies on children's cognitive processes. Later, this concept was developed and considered as a mechanism that provides adaptation to the social environment. It has also been studied clinically in children with autism, frontal lesions, and frontotemporal dementia patients (7-10). There are many tests used to assess the ToM. Implied test, deception test, metaphor and irony comprehension, picture sorting, and lastly, the reading the mind test that has been used frequently in recent years (11-13).

Based on all this information, in our study, we aimed to examine the ToM model, which is a model that has been studied in diseases such as dementia which could be related to the temporal lobe of the brain in tinnitus patients. Tinnitus is the perception of sound without any external stimulus (14). Temporary and reversible tinnitus can occur frequently in communities (15). However, persistent tinnitus is a highly distressing condition that can cause significant discomfort and even lead to stress (16). This study was planned based on the hypothesis that this distressing bodily complaint may affect individuals' ToM skills and lead to the emergence of dysfunctional metacognitive beliefs in the course of the disease. We examined ToM skills and metacognitive functions in patients with tinnitus by comparing them with healthy controls, which has not been previously investigated in the literature.

Methods

Ethical Procedure

After obtaining approval from the Tokat Gaziosmanpaşa University Ethics Committee holding the (number: 22-KAEK-175, date: 25.08.2022), the study was conducted in accordance with the Declaration of Helsinki guidelines.

Inclusion and Exclusion Criteria

This study was conducted prospectively. Patients diagnosed with tinnitus with normal otoscopic examination and normal hearing were informed about the study at the university hospital otolaryngology and head and neck surgery clinic. Those with pure tone thresholds <26 decibels (dB) at 4 frequencies (0.5, 1.0, 2.0, 4.0 kHz) were defined as having normal hearing. Signed informed consent forms were obtained from patients who agreed to participate in the study. The study included individuals who had received medical treatment and did not benefit, volunteered to participate, could read and write, could fill out the forms, and sign the written consent form. Individuals with sensorineural/conductive or mixed hearing loss, abnormal otoscopic examination, poor general condition, abnormal blood tests in the last six months, known psychiatric illness, alcohol/substance use disorder, neurodegenerative disease, and mental disabilities were excluded from the study. The same psychiatrist interviewed all patients. Patients with psychiatric disorders such as major depressive disorder, anxiety disorders, and body dysmorphic disorder, which could also be the cause of tinnitus, were also excluded. The healthy control group was selected from individuals who could match the tinnitus patient group in terms of age and gender with no psychiatric illness and/or alcohol/substance use disorder and had no tinnitus.

Data Collection Tools

During the initial interview with the participants, informed consent forms were signed, and demographic data forms were filled out. Subsequently, the Beck depression inventory (BDI), the metacognitive questionnaire (MCQ-30), the Reading the Mind in the Eyes Test (RMET), and the tinnitus handicap inventory (THI) were administered.

Demographic Data Form: This is a form created by the researchers in line with the objectives of the study. It includes personal demographic information such as age, marital status, education, and employment status. It also includes clinical assessment questions regarding previous and current psychiatric treatment, alcohol/substance use, and the presence of any medical condition requiring medical treatment.

Beck Depression Inventory: Developed by Beck et al. (17) to assess the presence and severity of depressive symptoms, BDI is a self-report scale consisting of 21 items that are scored on a scale of 0-3. The calculated total score is evaluated, and a higher total score indicates a greater level of depressive symptoms (18).

Metacognitive Questionnaire: The long form of the questionnaire was developed by Wells and Cartwright-Hatton (19) in 1997, followed by the development of a 30-item short form in 2004. The questionnaire examines the presence of worrying and intrusive thoughts, their causes, benefits, and drawbacks. Each item is scored on a scale of 1-4 and is evaluated in five subscales. An increase in the calculated total score indicates an increase in metacognitive activities (20).

Reading the Mind in the Eyes Test: Developed by Baron-Cohen et al. (6) in 1997 to assess individuals' ability to recognize emotions. The original version of the test includes 36 pictures with different facial expressions. The individual selects the expression that best describes the picture among the given options. The validity and reliability study of the scale was conducted in Turkish by Yıldırım et al. (21) in 2011. In the Turkish adaptation, the number of pictures was determined as 32. The individual undergoing the test selects the item which they believe best describes the expressions they see in the pictures based on their current mental/psychological state (21).

Tinnitus handicap inventory: This scale evaluates the extent to which tinnitus affects patients' mental, occupational, social, emotional, and physical functions and their treatment satisfaction. The Turkish validity and reliability study was conducted by Aksoy et al. (22) in 2007.

Statistical Analysis

The data was studied using the statistical software SPSS for Windows 20 (IBM Corp. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY). Demographic variables such as age, marital status, and education were presented as mean±standard deviation and percentage (%). The Chi-square test was used for the analysis of these data and clinical variables. For the analysis of the scores of the BDI, MCQ-30, and RMET scales used in the study, the tests of significance for the difference between two means and Mann-Whitney U tests were employed. The relationship between the scales applied to the patient group regarding tinnitus was evaluated using Spearman's and Pearson's correlation tests. A p-value less than 0.05 was considered statistically significant.

Results

Demographic Data Distribution of Participants:

A total of 120 patients diagnosed with tinnitus were interviewed for the study, and 90 patients who met the inclusion criteria were included. The patient group consisted of 48 females (53.33%) and 42 males (46.66%). The mean age of the patient group was 45.80±13.39 years, while the control group had a mean age of 41.88±12.53 years (p=0.062). Out of the patient group, 65 individuals (72.22%) were married, while 26 individuals (28.88%) had never married or were divorced. None of the participants in the patient group or the healthy control group had a current or previous diagnosis of psychiatric illness. The demographic data of the participants is presented in Table 1.

Distribution of Quantitative Variables of Participants:

For the analysis of RMET and MCQ-30 scores, both of which followed a normal distribution, a test of the significance of the difference between the two means was used. The number of correct answers on the RMET was found to be significantly lower in the patient group compared to healthy controls (p=0.002). The total score of MCQ-30 and the sub-dimension score of cognitive awareness were higher in healthy controls (p=0.047 and 0.003, respectively). For the analysis of BDI values which did not follow a normal distribution, the Mann-Whitney U test was used. No statistically significant difference was found between the patient and control groups (p=0.084). The analysis of the quantitative variables of the groups is presented in Table 2.

Logistic Regression Analysis:

In the multivariate logistic regression model, it was found that only the RMET had a significant effect on tinnitus (p=0.003). No significance was found for the other scales applied. The results of the multivariate logistic regression analysis of the patients are presented in Table 3.

Results of Correlation Analysis:

According to the results of Spearman's correlation analysis, there was a moderate positive correlation between BDI and MCQ-30 cognitive confidence and uncontrollability sub-dimensions in the patient group. Moderate correlations were found between the scores of THI and BDI, and of MCQ-30 uncontrollability danger and MCQ-30 need to control thoughts (Table 4).

Discussion

In our study where we examined the executive functions and metacognitive functions of individuals suffering from tinnitus, we found that the cognitive performance of the patients was reduced regardless of differences in depression scores. Additionally, we identified that the patients had impaired metacognitive functions in certain areas.

In the available literature, it has been reported that individuals with tinnitus struggle to cope with their condition, and there is an increased frequency of psychological complaints

Table 1. Demographic characteristics of participants

	Patient group with tinnitus n=90	Healthy control group n=70	P-value
Age (Mean±SD)	45.80±13.39	41.88±12.53	0.062
Gender (n)	48/42	44/26	0.293
(Female/male) (%)	(53.33/46.66)	(62.85/37.14)	
Marital status	65/13/12	30/33/7	**<0.001**
(Married/single/other) (%)	(72.22/14.44/13.33%)	(42.85/47.14/10)	
Educational level			
Basic literacy	7 (7.77%)	6 (8.57%)	
Primary school graduate	40 (44.44%)	10 (14.28%)	**0.010**
High school graduate	22 (24.44%)	16 (22.85%)	
University graduate	21 (23.33%)	37 (52.85%)	
University student	0	1 (1.42%)	
Working status (%)			
Full-time employment	23 (25.55%)	33 (47.14%)	
Irregular income job	7 (7.77%)	7 (10%)	**<0.001**
Unemployed	3 (3.33%)	3 (4.28%)	
Homemaker	35 (38.88%)	12 (17.14%)	
Student	6 (6.66%)	12 (17.14%)	
Retired	16 (17.77%)	3 (4.28%)	

Data are presented as n (%)

SD: Standard deviation

Table 2. Analysis of quantitative variables within the groups

	Patient group with tinnitus (n=90)	Healthy control group (n=70)		P-value
MCQ-30	Mean±SD	Mean±SD	F	
Positive belief	12.43±4.97	12.10±4.37	1.763	0.679
Cognitive confidence	13.45±5.62	12.05±4.80	1.639	0.115
Uncontrollability-danger	16.68±6.07	16.18±5.65	0.414	0.622
Cognitive awareness	18.24±4.72	15.92±4.14	**2.073***	**0.003***
The need to control the thoughts	12.08±3.82	10.97±3.24	3.040	0.071
Total score	72.66±16.43	67.36±14.88	**0.961***	**0.041***
RME	15.50±5.16	18.28±4.96	**0.618***	**0.002***
	Median	**Median**	**Z**	
BDI	12.29 (8.00±21.00)	11.48 (7.00±16.01)	-.1.481	0.139

The significance test for the difference between two means is shown in the top section of the table, while the Mann-Whitney U test in the lower section. The values provided in the top section of the table represent mean±standard deviation, while the values given in the lower section represent median values *p<0.05

SD: Standard deviation, MCQ-30: Metacognitive questionnaire, RME: Reading the Mind in the Eyes Test, BDI: Beck Depression Inventory

and disorders among these individuals (23-25). It has been shown that individuals who perceive tinnitus as a significant source of stress experience increased depressive symptoms and have higher rates of major depressive disorder (24). At the same time, as the difficulty in recognizing one's emotions increases, the negative impact of tinnitus on one's life also increases (26). Furthermore, it has been observed that some patients exhibit a significant increase in suicidal ideation and suicide attempts (25). The presence of tinnitus, as well as the psychological complaints it causes, has been reported to decrease the quality of life for these patients (27). The common result found in all these studies in the literature is that patients have difficulty in adapting to the presence of tinnitus. In our study, we found that although the depression scores of the patients did not increase, their cognitive performance was reduced. In other words, we observed that higher-level cognitive awareness such as thinking about thinking, social communication skills, recognizing emotions

Table 3. Impact of scales on tinnitus in the multivariate logistic regression model

	β	Sig.	Odds Ratio	95% confidence interval for the odds ratio	
				Lower	Upper
BDI	0.015	0.375	1.015	0.982	1.050
RME	-0.108	**0.003***	0.898	0.837	0.963
MCQ-30					
Positive belief	-0.004	0.971	0.996	0.818	1.213
Cognitive confidence	0.104	0.266	1.110	0.924	1.334
Uncontrollability-danger	-0.008	0.935	0.992	0.823	1.196
Cognitive awareness	0.170	0.080	1.185	0.980	1.432
The need to control the thoughts	0.077	0.496	1.081	0.865	1.350
Total score	-0.038	0.668	0.963	0.810	1.145

*p<0.05, BDI: Beck Depression Inventory, RME: Reading the Mind in the Eyes Test, MCQ-30: Metacognitive questionnaire

Table 4. Correlation analysis results

	BDI	MCQ-PB	MCQ-CC	MCQ-UD	MCQ-CA	MCQ-NCT	MCQ-total	RME	THI
BDI	1	0.086	**0.325***	**0.475***	-0.051	**0.287***	**0.347***	-0.024	**0.302***
MCQ-PB	0.086	1	0.072	0.191	**0.511***	**0.389***	**0.640***	-0.008	-0.066
MCQ-CC	**0.325***	0.072	1	**0.411***	0.054	**0.271***	**0.558***	-0.200	0.095
MCQ-UD	**0.475***	0.191	**0.411***	1	0.230*	**0.486***	**0.714***	-0.035	**0.290***
MCQ-CA	-0.051	**0.511***	0.054	**0.230***	1	**0.527***	**0.648***	0.006	-0.048
MCQ-NCT	**0.287***	**0.389***	**0.271***	**0.486***	0.527*	0.1	**0.750***	-0.096	**0.232***
MCQ-total	**0.347***	**0.640***	**0.558***	**0.714***	0.648*	0.750*	0.1	-0.087	0.141
RME	-0.024	-0.008	-0.200	-0.035	0.006	-0.096	-0.097	1	-0.070
THI	**0.302***	-0.066	0.095	**0.290***	-0.048	**0.232***	0.144	-0.070	1

Pearson and Spearman correlation analysis tests were used in the calculations. The table presents the "r" values

*p<0.05, BDI: Beck Depression Inventory, MCQ: Metacognitive questionnaire, PB: Positive belief, CC: Cognitive confidence, UD: Uncontrollability/danger, CA: Cognitive awareness, NCT: Need to control the thoughts, RME: Reading the Mind in the Eyes Test, THI: Tinnitus handicap inventory

from facial expressions, and being aware of what is on other people's minds had decreased (1,6). The fact that the patients' depression scores did not increase could be due to many reasons such as the scale we used, our control group, the patient group, and the use of a self-report scale, which is not consistent with the literature in this sense. RMET, which has been used as a test material reflecting metacognitive abilities in a broader sense, such as recognizing emotions from facial expressions and solving mental states, has been widely used in many studies (9-12). It has been shown that a deterioration in metacognitive abilities was associated with impaired social communication skills. In other words, a deterioration in metacognitive abilities is related to impaired social functioning and interpersonal relationships (6,9-12,21). Given these findings, it is believed that the impairment of metacognitive abilities in patients suffering from tinnitus could also affect their social performance, as well as their academic and occupational achievements. In the tinnitus group, we observed that the level of marriage was higher, the level of education was lower, and homemakers were in the majority, but it is not possible to make a clear conclusion. In our study, while the patients' depression scores did not increase, we found that their cognitive performance was reduced. The presence of tinnitus alone had an impairing effect on their cognitive performance. Further, it was determined that RMET performance could be a predictor for tinnitus. The findings of our study indicate that the metacognitive abilities of patients are impaired, and this impairment could also affect their social skills and serve as a precursor to the disease. However, since our study is the first of its kind in this area, the data obtained needs to be supported by further research.

Finally, we identified differences in specific domains of metacognitive functions in tinnitus patients compared to healthy controls. We also found that as the impact of tinnitus on patients' daily activities and lives increased, their metacognitive functions were more significantly impaired

in certain sub-dimensions. In a study conducted in this field, tinnitus patients were only evaluated with MCQ-30. The correlation between metacognitive beliefs and THI was studied. It was observed that the uncontrollability and danger sub-dimensions of metacognitive beliefs were moderately positively correlated with the THI (28).

It has been shown in previous studies that dysfunctional metacognitive beliefs are associated with difficulties in coping with chronic illnesses and can trigger the emergence of psychiatric disorders (29).

Dysfunctional metacognitive beliefs have been reported to be associated with mental distress, making it difficult for individuals to tolerate chronic illnesses and accept the illness, and even disrupting treatment adherence (29).

There is no study in the literature that compares tinnitus patients with healthy controls using the MCQ-30. In our results, like the findings of the study mentioned above, it was found that the THI and MCQ-30 were positively correlated with the uncontrollability and danger sub-dimensions (28). Only one article published in the literature states that tinnitus without hearing loss is protective for cognitive performance. This article evaluated cognitive performance (30). In literature, cognitive destruction is considered inevitable, especially in the presence of hearing loss. In our study, what we looked at was not cognitive performance, but high-level cognition, metacognition, thinking about thinking, or more importantly, social communication skills. From this perspective, tinnitus affects patients' daily lives more significantly, more dysfunctional metacognition comes into play, or the presence of dysfunctional metacognition increases the impact of tinnitus on their daily functioning. The fact that depressive symptoms and the presence of depression, known to affect both RMET performance and MCQ-30 results, did not influence our findings further enhanced the value of our results. In our results, the scores of the patients on BDI were not statistically different from those of the healthy controls.

When evaluating our study, certain limitations should be taken into account. First, the relatively small sample size represents a limitation. Additionally, the reliance on self-report scales, the lack of anxiety level assessments, and the absence of structured clinical interviews based on the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) for psychiatric diagnosis further constrain the study's findings. Moreover, it was not possible to determine whether the lower educational level, marital status, and unemployment rate observed in the patient group were consequences of the disease or inherent characteristics of the study participants. These limitations restrict the generalizability of our findings. Therefore, further research with larger sample sizes and more comprehensive assessments is needed to strengthen the existing literature in this field.

Conclusion

In conclusion, we found that the cognitive performance of the individuals suffering from tinnitus was impaired compared to the healthy controls. We also identified that these patients had a higher prevalence of dysfunctional metacognition in certain domains. These findings suggest that individuals with tinnitus could be psychologically affected, and it would be beneficial to conduct mental assessments during the initial examination, provide psychological and social support to the patients, and assist them in improving their communication skills.

Ethics

Ethics Committee Approval: After obtaining approval from the Tokat Gaziosmanpaşa University Ethics Committee holding the (number: 83116987-553, date: 5.08.2022).

Informed Consent: Signed informed consent forms were obtained from patients who agreed to participate in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.K.Ç., Concept: E.K.Ç., F.Ö., Design: F.Ö., Data Collection and/or Processing: B.Y.E., Analysis and/or Interpretation: B.Y.E., Literature Search: E.K.Ç., F.Ö., Writing: E.K.Ç., F.Ö.

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

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Main Points

- Tinnitus constitutes a significant source of stress and may lead to impairment in cognitive performance and metacognitive abilities in patients.
- The current study showed that the cognitive performance of the individuals suffering from tinnitus was impaired compared to the healthy controls and that these patients had a higher prevalence of dysfunctional metacognition in certain domains
- It is believed that the impairment of metacognitive abilities could affect social performance, academic, and professional achievements.
- Providing psychological and social support to individuals with tinnitus may be beneficial in assisting them to improve their communication skills.

References

1. Beaudoin C, Leblanc É, Gagner C, Beauchamp MH. Systematic review and inventory of theory of mind measures for young children. Front Psychol. 2020; 10: 2905. [Crossref]

2. Premack D, Woodruff G. Does the chimpanzee have a theory of mind? Behavioral and Brain Sciences. 1978; 1: 515-26. [Crossref]
3. Smogorzewska J, Szumski G, Grygiel P. Theory of mind goes to school: Does educational environment influence the development of theory of mind in middle childhood? PLoS One. 2020; 15: 0237524. [Crossref]
4. Dunlosky J, Metcalfe J. Metacognition. Washington, D.C.: Sage Publications; 2009. [Crossref]
5. Carruthers P, Williams DM. Model-free metacognition. Cognition. 2022; 225: 105117. [Crossref]
6. Baron-Cohen S, Wheelwright S, Hill J, Raste Y, Plumb I. The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. J Child Psychol Psychiatry. 2001; 42: 241-51. [Crossref]
7. Sayin A, Oral N, Utku C, Baysak E, Candansayar S. Theory of mind in obsessive-compulsive disorder: Comparison with healthy controls. Eur Psychiatry. 2010; 25: 116-22. [Crossref]
8. Orso B, Lorenzini L, Arnaldi D, Girtler N, Brugnolo A, Doglione E, et al. The role of hub and spoke regions in theory of mind in early alzheimer's disease and frontotemporal dementia. Biomedicines. 2022; 10: 544. [Crossref]
9. Özsoy F, Kuloğlu MM. Evalution of metacognitive functions in major depressive and panic disorder patients. J Contemp Med. 2017; 7: 42-9. [Crossref]
10. Corcoran R, Mercer G, Frith CD. Schizophrenia, symptomatology and social inference: investigating "theory of mind" in people with schizophrenia. Schizophr Res. 1995; 17: 5-13. [Crossref]
11. Frith CD, Corcoran R. Exploring "theory of mind" in people with schizophrenia. Psychol Med. 1996; 26: 521-30. [Crossref]
12. Drury VM, Robinson EJ, Birchwood M. "Theory of mind" skills during an acute episode of psychosis and following recovery. Psychol Med. 1998; 28: 1101-12. [Crossref]
13. Langdon R, Coltheart M. Mentalising, schizotypy, and schizophrenia. Cognition. 1999; 71: 43-71.
14. Baguley D, McFerran D, Hall D. Tinnitus. Lancet. 2013; 382: 1600-7. [Crossref]
15. Langguth B, Landgrebe M, Kleinjung T, Sand GP, Hajak G. Tinnitus and depression. World J Biol Psychiatry. 2011; 12: 489-500. [Crossref]
16. Hoffman HJ, Reed GW. Epidemiology of tinnitus. Snow JR, editor. Tinnitus: theory and management. Lewiston, NY: BC Decker; 2004. p. 16-41. [Crossref]
17. Beck At, Ward Ch, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961; 4: 561-71. [Crossref]
18. Hisli N. Beck depresyon envanterinin üniversite öğrencileri için geçerliliği, güvenilirliği. Psikoloji Dergisi. 1989; 7: 3-13. [Crossref]
19. Wells A, Cartwright-Hatton S. A short form of the metacognitions questionnaire: properties of the MCQ-30. Behav Res Ther. 2004; 42: 385-96. [Crossref]
20. Tosun A, Irak M. Üstbiliş Ölçeği-30'un Türkçe uyarlaması, geçerliği, güvenirliği, kaygı ve obsesif-kompülsif belirtilerle ilişkisi. Turk Psikiyatri Derg. 2008; 19: 67-80. [Crossref]
21. Yıldırım EA, Kaşar M, Güdük M, Ateş E, Küçükparlak I, Ozalmete EO. Investigation of the reliability of the "reading the mind in the eyes test" in a Turkish population. Turk Psikiyatri Derg. 2011; 22: 177-86. [Crossref]
22. Aksoy S, Firat Y, Alpar R. The tinnitus handicap inventory: a study of validity and reliability. Int Tinnitus J. 2007; 13: 94-8. [Crossref]
23. Mazurek B, Boecking B, Brueggemann P. Association between stress and tinnitus-new aspects. Otol Neurotol. 2019; 40: e467-73. [Crossref]
24. Hackenberg B, Döge J, O'Brien K, Bohnert A, Lackner KJ, Beutel ME, et al. Tinnitus and its relation to depression, anxiety, and stress-a population-based cohort study. J Clin Med. 2023; 12: 1169. [Crossref]
25. Szibor A, Mäkitie A, Aarnisalo AA. Tinnitus and suicide: An unresolved relation. Audiol Res. 2019; 9: 222. [Crossref]
26. Kaya Çelik E, Özsoy F, Yıldız M. Depression, Alexithymia Levels, and Somatization in Patients with Tinnitus. Med J West Black Sea. 2023; 7: 289-95. [Crossref]
27. Zeman F, Koller M, Langguth B, Landgrebe M. Tinnitus research initiative database study group. Which tinnitus-related aspects are relevant for quality of life and depression: results from a large international multicentre sample. Health Qual Life Outcomes. 2014; 12: 7. [Crossref]
28. Natalini E, Fioretti A, Riedl D, Moschen R, Eibenstein A. Tinnitus and metacognitive beliefs-results of a cross-sectional observational study. Brain Sci. 2020; 11: 3. [Crossref]
29. Lenzo V, Sardella A, Martino G, Quattropani MC. A systematic review of metacognitive beliefs in chronic medical conditions. Front Psychol. 2020; 10: 2875. [Crossref]
30. Hamza Y, Zeng FG. Tinnitus is associated with improved cognitive performance in non-hispanic elderly with hearing loss. Front Neurosci. 2021; 15: 735950. [Crossref]

Bilateral Endoscopic Type 1 Tympanoplasty in a Single Session: Functional and Clinical Outcomes

Original Investigation

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Abstract

Objective: This study aims to evaluate the functional and clinical outcomes of single-session bilateral endoscopic type 1 tympanoplasty, with a focus on postoperative (post-op) hearing improvement and graft success rates in patients with chronic otitis media and tympanic membrane perforations.

Methods: Fifteen patients (30 ears) with bilateral dry tympanic membrane perforations underwent trans-canal endoscopic type 1 tympanoplasty using a tragal perichondrium graft. Preoperative (pre-op) and post-op audiometric data, including pure-tone averages (PTAs) and air-bone gap (ABG) measurements at various frequencies, were collected and analyzed.

Results: Functional success was defined as a post-op ABG <20 dB and PTA level improvements, while clinical success was determined by the presence of an intact tympanic membrane graft. The mean pre-op ABG significantly decreased post-oply in both ears, with an average ABG improvement of 25.00±7.32 dB at 500 Hz in the right ear and 18.00±8.41 dB in the left ear. The post-op PTA demonstrated an average gain of 27.00±7.51 dB in the right ear and 29.33±6.23 dB in the left ear. The functional success rate, defined as a post-op ABG <20 dB, was 93.33%, while clinical success, based on graft integrity, was also 93.33%.

Conclusion: Single-session bilateral endoscopic tympanoplasty is a safe and effective procedure with high functional and clinical success rates. It leads to significant hearing improvement and has minimal post-op complications.

Keywords: Tympanoplasty, endoscopic surgery, chronic otitis media, perichondrium, hearing improvement, surgical outcomes

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Introduction

Chronic otitis media (COM) is a prevalent otologic condition that may lead to lasting alterations in the tympanic membrane and middle ear anatomy (1,2). Tympanoplasty, a surgical procedure designed to reconstruct the tympanic membrane and restore hearing, is a standard treatment for these alterations (3,4). Various techniques exist, including postauricular, endaural, and transcanal approaches, with grafting materials such as fat, cartilage, perichondrium, and temporalis fascia (5-8). Minimally invasive endoscopic techniques have gained popularity in recent years due to their ability to provide a broader field of view and improved access

to challenging anatomical areas. This is especially beneficial for managing chronic otitis, as endoscopy allows for better visualization of the attic, hypotympanum, and facial recess (7,9,10).

Traditionally, bilateral tympanic membrane perforations have been repaired in separate surgeries, leading to increased costs, longer operative times, and greater patient discomfort. Single-session bilateral tympanoplasty offers a more efficient and convenient option, though concerns over postoperative (post-op) complications, including iatrogenic hearing loss (with an estimated risk of 1.2% to 4.5%), have limited its adoption (11-13). This study aims to assess the functional and anatomical outcomes of patients undergoing single-session bilateral endoscopic transcanal tympanoplasty, focusing on hearing improvement and graft integrity. By analyzing these outcomes, this research highlights the effectiveness of a minimally invasive approach in achieving significant clinical and functional success rates.

Methods

Study Design and Participants

This study was designed as a retrospective, single-center investigation conducted in the otorhinolaryngology department of a tertiary care hospital over an 18-month period from January 2023 to June 2024. Fifteen patients (30 ears) underwent bilateral endoscopic type 1 tympanoplasty due to conductive hearing loss associated with COM and tympanic membrane perforation. Patients selected for the study had sufficiently large external auditory canals, and none had undergone previous revision surgeries. Patients requiring prosthetic materials for ossicular chain reconstruction were excluded from the analysis.

All procedures were performed using a transcanal endoscopic approach with a tragal perichondrium graft, utilizing the over-underlay technique. All participants provided written informed consent for the surgical procedures and study participation. The study protocol received ethical approval from the Ministry of Health of the Republic of Azerbaijan, Azerbaijan State Advanced Training Institute for Doctors, named after A. Aliyev Local Ethics Committee approved this study (decision no: EaR. No:1/09.02.2024-2/II, date: 09.02.2024), and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Surgical Procedures and Follow-up

The study included 30 ears from patients with bilateral dry tympanic membrane perforations. A single surgeon performed all surgeries, ensuring standardized techniques and reliable outcomes. General anesthesia was administered to all patients, with no cases requiring sedation. The surgeries were conducted using a transcanal approach with endoscopic assistance, utilizing a 0-degree endoscope. None of the patients exhibited ossicular chain disruption, mastoid pathology, or other middle or inner ear abnormalities. A prerequisite for surgery was a minimum dry ear period of two months, which all patients met.

In all cases, grafting was performed using the over-underlay technique, and tragal perichondrium served as the graft material. The ear with poorer hearing, as determined by preoperative (pre-op) audiometric evaluations, was operated on first. Post-oply, the ear canal was packed with gel foam and gauze soaked in a mixture of hydrocortisone and nitrofurazone cream, which was retained for one week. This post-op packing protocol was applied uniformly across all patients. Follow-up evaluations were conducted at 2 and 4 weeks, during which otomicroscopic examinations were performed. Audiometric assessments were carried out approximately three months post-surgery.

Data Collection and Evaluation

Demographic and audiometric data were collected pre-oply and post-oply. Each patient underwent a bilateral, single-session Type 1 tympanoplasty. Pre-op assessments included computed tomography and audiometric evaluations, while post-op audiometry was performed at a minimum follow-up of three months. The ear with poorer hearing (based on pre-op pure-tone audiometry results) was operated on first, followed by the contralateral ear. Audiometric evaluations were conducted using appropriate masking techniques, and pure-tone average (PTA) values were calculated across four frequencies (0.5, 1, 2, and 4 kHz) pre-oply and post-oply. There are various techniques to measure functional and clinical success after tympanoplasty (13-15). Post-op results were only included if they were collected at least three months after surgery.

Hearing loss was categorized using the American Speech-Language-Hearing Association (ASHA) classification for “type, degree, and configuration of hearing loss” The classification was as follows:

- Normal hearing: -10 to 15 dB HL
- Slight hearing loss: 16 to 25 dB HL
- Mild hearing loss: 26 to 40 dB HL
- Moderate hearing loss: 41 to 55 dB HL
- Moderately severe hearing loss: 56 to 70 dB HL
- Severe hearing loss: 71 to 90 dB HL
- Profound hearing loss: >91 dB HL

A PTA of 25 dB or lower was considered indicative of functional hearing. Pre-op and post-op hearing thresholds were compared to determine the percentage of improvement and establish the functional success rate (16,17).

The air-bone gap (ABG) was calculated by subtracting bone conduction (BC) thresholds from air conduction (AC) thresholds at 0.5, 1, 2, and 4 kHz. ABG gain, representing hearing improvement, was calculated as the difference between pre-op and post-op ABG values at these frequencies. A post-op ABG of ≤20 dB was defined as "success", while an ABG >21 dB was categorized as "not successful" (18,19).

Anatomical (clinical) success was assessed based on the condition of the tympanic membrane during post-op follow-ups. Tympanic membrane integrity was examined, and success was defined by whether the membrane remained intact. The rate of tympanic membrane preservation was calculated based on these follow-up examinations.

Statistical Analysis

Various statistical methods were employed to evaluate audiometric outcomes and assess clinical and functional success. Key audiometric data, including pre-op and post-op PTA and ABG values at 0.5, 1, 2, and 4 kHz, were summarized using descriptive statistics presented as mean±standard deviation (SD). Data normality was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Based on these assessments, appropriate parametric statistical methods were selected for further analysis.

Variance homogeneity was verified using Levene's test. For within-group comparisons of pre-op and post-op PTA and ABG values, the paired-sample t-test was used. This test is ideal for analyzing changes over time in the same patient group, making it particularly relevant for this study. A p-value of <0.05 was considered statistically significant, and exact p-values were reported for clarity.

Results

Fifteen patients, comprising 30 ears, underwent single-session bilateral Type 1 tympanoplasty. Of these patients, 8 (53.33%) were female, and 7 (46.67%) were male, with a mean age of 39.3±6.40 years at the time of surgery. The mean follow-up period was 10.33±3.31 months, ranging from 5 to 15 months. The operation times were not recorded separately for each ear; however, the average duration for bilateral simultaneous surgeries was approximately 120±28 minutes, based on typical timelines for such procedures.

Audiometric Parameters

For the right ear, the pre-op ABG at 500 Hz was 35.33±8.96 dB, which showed significant improvement post-op, reducing to 10.33±5.50 dB (p<0.002). The mean ABG gain at this frequency was 25.00±7.32 dB. At 1000 Hz, the pre-op ABG of 34.67±7.43 dB improved to 14.00±6.04 dB post-oply (p<0.002), with a mean gain of 20.67±9.61 dB. At 2000 Hz, the ABG decreased from 44.67±7.43 dB pre-oply to 20.00±5.98 dB post-oply (p<0.000), yielding a gain of 24.67±6.94 dB. At 4000 Hz, the ABG improved from 33.33±6.99 dB pre-oply to 15.33±4.42 dB post-op ly (p<0.001), with a corresponding gain of 18.00±8.62 dB.

For the left ear, the pre-op ABG at 500 Hz was 29.67±9.35 dB, improving significantly to 11.67±4.50 dB post-oply (p<0.001), resulting in a mean gain of 18.00±8.41 dB. At 1000 Hz, the pre-op ABG of 39.67±7.43 dB decreased to 15.67±7.04 dB post-oply (p<0.004), with a gain of 24.00±10.72 dB. At 2000 Hz, the ABG improved from 48.00±8.62 dB pre-oply to 19.67±6.11 dB post-oply (p<0.000), yielding a gain of 28.33±8.38 dB. At 4000 Hz, the ABG improved from 28.67±5.50 dB pre-oply to 13.67±5.50 dB post-oply (p<0.001), with a corresponding gain of 15.00±9.06 dB (Table 1).

In the left ear, similar improvements were observed. The pre-op ABG at 500 Hz was 29.67±9.35 dB, which improved significantly to 11.67±4.50 dB post-oply (p<0.001), resulting in a mean gain of 18.00±8.41 dB. At 1000 Hz, the pre-op ABG of 39.67±7.43 dB decreased to 15.67±7.04 dB post-oply (p<0.004), with a gain of 24.00±10.72 dB. At 2000 Hz, the ABG improved from 48.00±8.62 dB pre-oply to 19.67±6.11 dB post-oply (p<0.000), yielding a gain of 28.33±8.38 dB. Similarly, at 4000 Hz, the ABG improved from 28.67±5.50 dB pre-oply to 13.67±5.50 dB post-oply (p<0.001), with a corresponding gain of 15.00±9.06 dB (Table 1).

The pre-op PTA in the right ear was 42.00±7.51 dB, which significantly improved to 15.00±5.35 dB post-oply (p<0.002), reflecting a mean PTA gain of 27.00±7.51 dB. For the left ear, the pre-op PTA was 43.33±6.45 dB, which improved significantly to 14.00±4.71 dB post-oply (p<0.000), with a PTA gain of 29.33±6.23 dB.

Functional and Clinical Outcomes

The functional success rate, defined as achieving a post-op ABG of <20 dB, was 93.33%, corresponding to 14 out of 15 patients for both the right and left ears (28 ears in total). In terms of hearing improvement, all 15 patients (100%) achieved functional hearing bilaterally, defined as slight or normal hearing levels post-op ly.

Before surgery, 11 patients (73.33%) had moderate hearing loss in the right ear, and 12 patients (80%) had moderate hearing loss in the left ear. After surgery, 12 patients (80%) achieved normal hearing, while three patients (20%) had slight hearing loss in the right ear. For the left ear, 13 patients (86.67%) achieved normal hearing, while two patients (13.33%) had slight hearing loss. These findings indicate a significant shift from moderate hearing loss to either normal hearing or slight hearing impairment, as confirmed by statistical analysis (p<0.005).

Anatomical success, characterized by tympanic membrane integrity and graft uptake, was achieved in 14 out of 15 patients (93.33%) for both ears. This corresponds to an overall

anatomical success rate of 93.33%, as detailed in Table 2. No patients experienced post-op sensorineural hearing loss or deterioration in BC. No major surgical complications were observed during the post-op period, confirming the safety and efficacy of the procedure.

Discussion

Tympanoplasty is a commonly performed procedure in otologic surgery. Recently, minimally invasive techniques, particularly endoscopic approaches, have gained prominence across many surgical fields, including otology (1-5). While microscopic techniques allow for the use of both hands and provide a three-dimensional view, they are limited when visualizing anterior perforations. Endoscopic tympanoplasty overcomes this limitation by offering a wider field of view, particularly with angled scopes, which enhance visualization of difficult-to-reach areas, such as the anterior tympanic membrane, attic, and facial recess. This technique is especially beneficial for patients with narrow ear canals, anterior perforations, or obstructive bony structures (4,5).

While this study highlights the significant benefits of endoscopic tympanoplasty, including enhanced visualization, minimal tissue trauma, and improved cosmetic outcomes, it is essential to critically evaluate its advantages and limitations compared to microscopic tympanoplasty. The endoscopic approach provides a wider field of view, particularly for accessing anatomically challenging areas such as the anterior tympanic membrane, attic, and facial recess. However, the technique has certain limitations, such as the lack of binocular vision and the necessity of single-handed operation, which can pose challenges for less experienced surgeons. These drawbacks can be partially mitigated using a high-definition camera system or endoscope holder (4,7,9).

On the other hand, the microscopic approach offers distinct advantages, such as binocular vision, depth perception, and the ability to use both hands freely during surgery. These

Table 1. Audiometric parameters in single-sitting bilateral tympanoplasty

Parameter	Ear	500 Hz	1000 Hz	2000 Hz	4000 Hz	PTA
Pre-operative ABG	Right ear	35.33±8.96	34.67±7.43	45.00±7.79	33.33±6.99	42.00±7.51
Left ear	29.67±9.35	39.67±7.43	48.00±8.62	28.67±5.50	43.33±6.45	
Post-op ABG	Right ear	10.33±5.50	14.00±6.04	20.00±5.98	15.33±4.42	15.00±5.35
Left ear	11.67±4.50	15.67±7.04	19.67±6.11	13.67±5.50	14.00±4.71	
Pre-post ABG p-value	Right ear	p<0.002	p<0.002	p<0.000	p <0.001	p<0.002
	$p=2.85\times10^{-10}$	$p=2.14\times10^{-9}$	$p=6.56\times10^{-11}$	$p=1.79\times10^{-9}$	$p=2.78\times10^{-12}$	
Left ear	p<0.001	p<0.004	p<0.000	p <0.001	p<0.000	
	$p=1.35\times10^{-7}$	$p=3.86\times10^{-10}$	$p=2.08\times10^{-11}$	$p=1.35\times10^{-7}$	$p=1.23\times10^{-14}$	

ABG: Air-bone gap, PTA: Pure tone average, dB: Decibel, SD: Standard deviation, Frequencies: 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz

Table 2. Functional and clinical success of the bilateral single-sitting tympanoplasty

Parameters		Right ear (± SD)	Left ear (± SD)	Total ear (± SD)
ABG	**Mean (dB)**	14.92±3.79	15.17±3.86	15.05±3.82
	Success (Number of patients)	14 patients (93.33%)	14 patients (93.33%)	28 patients (93.33%)
PTA	**Pre-op mean (dB)**	42.00±7.51	43.33±6.45	42.67±6.98
	Pre-op mean (dB)	15.00±5.35	14.00±4.71	14.50±5.03
	Gain (total±SD)	27.00±7.51	29.33±6.23	28.17±6.87
Hearing success (number of patients)		15 patients (100%)	15 patients (100%)	30 patients (100%)
Pre-op	**Moderate hearing loss**	11 patients (73.33%)	12 patients (80%)	23 patients (76.67%)
	Mild hearing loss	4 patients (26.67%)	3 patients (20%)	7 patients (23.33%)
Post-op	**Slight hearing loss**	3 patients (20%)	2 patients (13.33%)	5 patients (16.67%)
	Normal hearing	12 patients (80%)	13 patients (86.67%)	25 patients (83.33%)
Clinical success (number of patients)		14 patients (93.33%)	14 patients (93.33%)	28 patients (93.33%)

ABG: Air-bone gap, PTA: Pure tone average, dB: Decibel, SD: Standard deviation, pre-op: Pre-operative, post-op: Post-operative

features make it particularly effective for managing larger perforations and achieving precise graft placement. However, microscopic tympanoplasty often requires postauricular incisions or canaloplasty, which may result in longer operative times, increased tissue trauma, and less favorable cosmetic outcomes (20,21).

A comparative analysis of the findings from this study with previously published literature provides further insight into the observed outcomes and highlights distinct differences. In the present study, the functional success rate, defined by achieving a post-op ABG <20 dB, was 93.33%. This was accompanied by substantial hearing improvements, reflected in a mean PTA gain of 28.17±6.87 dB, and an anatomical success rate of 93.33%, indicating intact tympanic membrane grafts in the majority of cases. These outcomes align closely with the results reported by Maran et al. (20), who documented graft success rates of 90% for endoscopic tympanoplasty and 96.67% for microscopic tympanoplasty. Nevertheless, Maran et al. (20) noted that the microscopic approach yielded slightly superior outcomes in cases involving larger perforations, underscoring the critical role of enhanced depth perception provided by microscopic techniques in achieving precise graft placement.

In terms of operative time, our findings align with existing literature. Our study's average endoscopic tympanoplasty duration was approximately 120±28 minutes for bilateral cases. Maran et al. (20) reported shorter operative times for the endoscopic approach (65.5±3.45 minutes) compared to the microscopic method (85.7±3.42 minutes) for unilateral procedures, highlighting the efficiency of the endoscopic technique.

Post-op outcomes also favor the endoscopic approach in terms of patient recovery. Our study demonstrated quicker recovery times and reduced post-op discomfort due to the minimally invasive transcanal approach, which avoids postauricular incisions. Similarly, Maran et al. (20) noted less post-op pain and superior cosmetic outcomes with endoscopic tympanoplasty.

Despite these advantages, the limitations of endoscopic tympanoplasty should not be overlooked. The steep learning curve, reliance on a two-dimensional view, and potential risks from heat generated by the light source underscore the need for adequate training and caution (18,21). Future studies with larger sample sizes and direct comparisons must fully elucidate each approach's relative merits.

While our findings support the efficacy and safety of endoscopic tympanoplasty for bilateral cases, both techniques have unique advantages. The approach should be tailored to the patient's anatomy and the surgeon's expertise, with further research needed to optimize outcomes for specific clinical scenarios. The endoscopic approach reduces operative time, improves cosmetic outcomes, and results in less post-op pain and reduced post-op care requirements (20,21). In our study, using a zero-degree endoscope in transcanal tympanoplasty allowed for a minimally invasive procedure without postauricular incisions or canal drilling. This preserved the middle ear's anatomy and reduced the risks associated with more invasive methods.

Previous studies, such as Ayache's work (22), reported a 96% graft closure rate in endoscopic tympanoplasty using cartilage grafts, comparable to our study's anatomical success rate of 93.33%. Furthermore, significant improvements were observed in post-op ABG, mirroring findings from other studies, which reported similar reductions in ABG.

Endoscopic tympanoplasty has its limitations. Operating with one hand and using a two-dimensional view can be challenging, particularly for surgeons still gaining experience. The learning curve for this technique is steep, and small-diameter endoscopes can restrict the wide-angle views, a primary advantage of the endoscopic approach. Additionally, heat from the light source, particularly xenon lights, can pose risks, although adjusting the light's intensity can mitigate this concern (23).

The cost-effectiveness of same-day bilateral tympanoplasty stands out as a key advantage, particularly when conducting the surgeries in separate sessions. In this study, the single-session bilateral approach demonstrated a remarkable reduction in total expenses, lowering costs by approximately 40-50% relative to separate procedures. In the context of Azerbaijan, where the cost of a single tympanoplasty procedure-including hospital stay, anesthesia, and surgical fees-ranges between 800 and 1200 AZN (equivalent to 500-700 USD), this cost-saving approach offers significant financial relief. By consolidating both surgeries into one session, patients and their families benefit from substantial economic savings, effectively reducing the financial burden on both individual households and the broader healthcare system.

Additionally, the economic advantages extend beyond direct medical costs. Indirect savings are realized through reduced transportation expenses, as fewer visits to healthcare facilities are required. Furthermore, patients experience fewer work absences, which is particularly beneficial for those in the workforce, and the streamlined nature of post-op care minimizes the complexities associated with recovery. These combined factors highlight the dual financial and logistical benefits of same-day bilateral tympanoplasty, making it an attractive option in resource-limited settings while maintaining high standards of clinical care.

Daneshi et al. (13) found that single-session bilateral tympanoplasty reduces costs by 55% and shortens

hospitalization. Our study showed 93.33% graft success, a PTA gain of 28.17±6.87 dB, and post-op ABG <20 dB in 93.33% of cases, similar to their results. Operative time was 120±28 minutes in our study, compared to 90±10 minutes in theirs. Both studies highlight the efficiency of same-day bilateral tympanoplasty. Our endoscopic approach avoided postauricular incisions, speeding recovery. Graft material selection varied, but both methods had high success rates. Same-day tympanoplasty offers cost savings and excellent outcomes. Future studies should refine techniques and compare grafts.

Our study has certain limitations. The small sample size limits the generalizability of the results, and the study's retrospective nature introduces potential biases in data collection. Moreover, the steep learning curve for surgeons using endoscopic techniques may restrict the widespread adoption of this method. Future studies with larger sample sizes and randomized controlled designs are needed to confirm these findings and further explore the benefits and limitations of endoscopic tympanoplasty.

Conclusion

This study demonstrated the efficacy and safety of performing bilateral single-session type 1 tympanoplasty using a transcanal endoscopic approach. The procedure led to significant improvements in Hearing, as shown by reduced ABGs and a high functional success rate of 93.33%. Additionally, clinical success was achieved in 93.33% of cases, with no reported complications such as iatrogenic sensorineural hearing loss. These findings suggest that bilateral tympanoplasty in a single session is a viable and effective treatment option for patients with COM, offering substantial clinical benefits. Our study supports using the transcanal endoscopic technique as a minimally invasive, effective, and safe approach for bilateral tympanoplasty, especially in appropriately selected patients.

Ethics

Ethics Committee Approval: The study protocol received ethical approval from the Ministry of Health of the Republic of Azerbaijan, Azerbaijan State Advanced Training Institute for Doctors, named after A.Aliyev Local Ethics Committee approved this study (decision no: EaR. no:1/09.02.2024-2/II, date: 09.02.2024), and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: All participants provided written informed consent for the surgical procedures and study participation.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.A., Concept: A.A., R.H., Design: A.A., R.H., Data Collection or Processing: A.A., Analysis or Interpretation: A.A., Literature Search: A.A., R.H., Writing: A.A., R.H.

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

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Main Points

- This study is the first to evaluate the outcomes of single-session bilateral endoscopic Type 1 tympanoplasty. The findings provide a comprehensive assessment of the procedure's functional and clinical success rates, establishing a foundational understanding of its efficacy in this region.
- The study demonstrates a high success rate, with significant postoperative improvements in ABG and PTA thresholds. Functional success, defined as a post-op ABG <20 dB, and clinical success, determined by intact tympanic membrane grafts, were achieved in 93.33% of cases.
- By utilizing a transcanal endoscopic approach, this study highlights the advantages of a minimally invasive technique, including shorter operative times, cost savings, and faster patient recovery compared to traditional methods. This approach minimizes surgical trauma and postoperative complications, emphasizing its potential for broader clinical adoption.

References

1. Gökharman FD, Şenbil DC, Aydin S, Karavaş E, Özdemir Ö, Yalçın AG, et al. Chronic otitis media and middle ear variants: is there a relation? World J Clin Cases. 2023; 11: 3481-90. [Crossref]
2. Khairkar M, Deshmukh P, Maity H, Deotale V. Chronic suppurative otitis media: a comprehensive review of epidemiology, pathogenesis, microbiology, and complications. Cureus. 2023; 15: 43729. [Crossref]
3. Nicholas Jungbauer W Jr, Jeong S, Nguyen SA, Lambert PR. Comparing myringoplasty to type I tympanoplasty in tympanic membrane repair: a systematic review and meta-analysis. Otolaryngol Head Neck Surg. 2023; 168: 922-34. [Crossref]
4. Aliyeva A, Hashimli R. Endoscopic type 1 tympanoplasty: evaluation of clinical success and hearing improvement. Medeniyet Med J. 2024; 39: 268-74 [Crossref]
5. Bayram A, Bayar Muluk N, Cingi C, Bafaqeeh SA. Success rates for various graft materials in tympanoplasty-a review. J Otol. 2020; 15: 107-11. [Crossref]
6. Park SY, Lee HJ, Shim MJ, Kim DK, Suh BD, Park SN. Swing-door overlay tympanoplasty: surgical technique and outcomes. Clin Exp Otorhinolaryngol. 2018; 11: 186-91. [Crossref]

7. Crotty TJ, Cleere EF, Keogh IJ. Endoscopic versus microscopic type-1 tympanoplasty: a meta-analysis of randomized trials. Laryngoscope. 2023; 133: 1550-7. [Crossref]
8. Jumaily M, Franco J, Gallogly JA, Hentzelman JL, Costa DJ, Wild APK, et al. Butterfly cartilage tympanoplasty outcomes: a single-institution experience and literature review. Am J Otolaryngol. 2018; 39: 396-400. [Crossref]
9. Bianchini AJ, Berlitz VG, Mocelin AG, Ribeiro JF, Keruk JG, Hamerschmidt R. Endoscopic or microscopic tympanoplasty advantages and disadvantages: a theory domain systematic review. Int Arch Otorhinolaryngol. 2022; 27: 528-35. [Crossref]
10. Takahashi M, Motegi M, Yamamoto K, Yamamoto Y, Kojima H. Endoscopic tympanoplasty type I using interlay technique. J Otolaryngol Head Neck Surg. 2022; 51: 45. [Crossref]
11. Raghuwanshi SK, Asati DP. Outcome of single-sitting bilateral type 1 tympanoplasty in Indian patients. Indian J Otolaryngol Head Neck Surg. 2013; 65: 622-6. [Crossref]
12. Umamaheswaran P, Mohanty S, Manimaran V, Jayagandhi S, Jeyabalakrishnan SP. A comparative study of sequential vs. simultaneous type I tympanoplasty in patients with bilateral chronic otitis media-Mucosal type. J Otol. 2020; 15: 59-61. [Crossref]
13. Daneshi A, Jahandideh H, Daneshvar A, Safdarian M. Bilateral same-day endoscopic transcanal cartilage tympanoplasty: initial results. Braz J Otorhinolaryngol. 2017; 83: 411-5. [Crossref]
14. Wu X, Zhang Q, Huang Y, Wang X, Feng G. Predictors of functional outcomes and recovery time following tympanoplasty. Ear Nose Throat J. 2023: 01455613231194748. [Crossref]
15. Zhu XH, Zhang YL, Xue RY, Xie MY, Tang Q, Yang H. Predictors of anatomical and functional outcomes following tympanoplasty: a retrospective study of 413 procedures. Laryngoscope Investigative Otolaryngology. 2021; 6: 1421-8. [Crossref]
16. 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: 186-7. [Crossref]
17. Çelik Ç, Ceylan ME, Aliyeva A, Düzenli U, Dalgıç A. The effect of perioperative i.v. corticosteroids on hearing outcome following stapedotomy. ENT Updates. 2018; 8: 82-7. [Crossref]
18. Aliyeva A, Hepkarsi S. Optimal grafting methods in endoscopic type 1 tympanoplasty: a comprehensive guide. Indian J Otolaryngol Head Neck Surg. 2024; 5: 1-8. [Crossref]
19. Ceylan ME, Dalğıç A, Aliyeva A, Çelik Ç, Yıldız MT, Olgun L. Functional and symmetrical hearing after bilateral stapes surgery. B-ENT. 2023; 19: 44-9. [Crossref]
20. Maran RK, Jain AK, Haripriya GR, Jain S. Microscopic versus endoscopic myringoplasty: a comparative study. Indian J Otolaryngol Head Neck Surg. 2019; 71: 1287-91. [Crossref]
21. Hashim ND, Lee SA, Jang SH, Moon IS. A comparison of endoscopic and microscopic inlay butterfly cartilage tympanoplasties and their educational utility. PLoS One. 2020; 15: 0241152. [Crossref]
22. Ayache S. Cartilaginous myringoplasty: the endoscopic transcanal procedure. Eur Arch Otorhinolaryngol. 2013; 270: 853-60. [Crossref]
23. Monteiro EMR, Beckmann S, Pedrosa MM, Siggemann T, Morato SMA, Anschuetz L. Learning curve for endoscopic tympanoplasty type I: comparison of endoscopic-native and microscopically-trained surgeons. Eur Arch Otorhinolaryngol. 2021; 278: 2247-52. [Crossref]

Validity of the Turkish Version of the Tinnitus Primary Function Questionnaire

Original Investigation

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Abstract

Objective: This study aimed to evaluate the reliability and validity of the Turkish version of the Tinnitus Primary Function Questionnaire (TPFQ-T).

Methods: The study was conducted with 103 patients who had been experiencing tinnitus for longer than three months. All participants completed the TPFQ-T, the Beck Anxiety Inventory, the Beck Depression Inventory, the Pittsburgh sleep quality index, the Tinnitus Handicap Inventory and the magnitude estimation.

Results: Cronbach's alpha was 0.88. Cronbach's alpha was also computed for every one of the four subscales: a=0.67 for sleep, a=0.72 for hearing, a=0.86 for concentration, and a=0.75 for emotion. There was a correlation between the overall score obtained from the TPFQ-T and its subcategories and other questionnaires measuring corresponding factors.

Conclusion: Overall, the findings of this investigation show that the TPFQ-T is both reliable and valid. As a result, the current translated version of the TPFQ-T is suitable for patients who speak Turkish as their first language and serves as an effective tinnitus questionnaire.

Keywords: Tinnitus, questionnaire, validity, quality of life

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Introduction

The sense of hearing a sound such as pure tone, noise, or hissing in the absence of an objective, physical source is known as tinnitus (1). Tinnitus is a prevalent clinical symptom with numerous intricate reasons. Given its subjective nature, self-reported questionnaires have become more common in recent decades for evaluating the condition. Tinnitus questionnaires are a popular tool for guiding treatment and evaluating tinnitus research (2). The purpose of tinnitus questionnaires is to accurately identify and measure the patient's tinnitus-related problems. The study by Tyler and Baker (3) in 1983 is perhaps the first systematic investigation of tinnitus utilizing the self-report approach.

Worldwide, several questionnaires are in widespread use. Presently there are two scales that have been translated into

Turkish (4,5). The most used is the Tinnitus Handicap Inventory (THI), but this questionnaire cannot help to distinguish between different responses (4). Although it has been suggested that it is less sensitive to variations during therapy, it was created expressly to diagnose the severity of the condition. Moreover, the three-label category scale has no practical application in the management of tinnitus (2).

Tyler et al. (6) developed the Tinnitus Primary Function Questionnaire (TPFQ), which is being widely used internationally, for research and treatment purposes. Since each item is rated on an interval scale ranging from 0 to 100, it is more likely to identify small variations (2).

The TPFQ has been validated in multiple languages (2,6-10). Therefore, this study aimed to evaluate the validity and reliability of the TPFQ Turkish version (TPFQ-T).

Methods

A total of 103 participants, aged between 18 and 76 years (mean: 45.28±14.35 years), were included in the study. The sample size was determined based on recommendations in the literature, which suggest obtaining 5-10 times the number of scale items for cross-cultural adaptation studies (11). The study received ethical approval from the Health Sciences University Non-Interventional Research Ethics Committee (decision no: 19/222, dated: 28/05/2019), and permission was obtained from Dr. Tyler via email for the translation of the TPFQ.

All patients had subjective, persistent, spontaneous, unilateral or bilateral subjective idiopathic tinnitus, with or without hearing loss. A detailed physical examination and pure-tone audiometry were conducted in the Otorhinolaryngology and Audiology Departments. Patients were included in the study if they had a tinnitus history of at least three months, unilateral or bilateral tinnitus, with or without hearing loss, and were fluent in Turkish. Those with any history of otologic or neurotologic surgery, as well as those with a history of behavioral, psychiatric, or neurological disorders were excluded.

Participants were asked to freely fill out the TPFQ-T. Additionally, they filled out four validated Turkish versions of related questionnaires: the THI, the Beck Depression Inventory (BDI), the Beck Anxiety Inventory (BAI), the Pittsburgh sleep quality index (PSQI) and the magnitude estimation. All questionnaires were used to assess the reliability and construct validity of the TPFQ-T.

The study was built upon the following consecutive phases:

Step 1: Translation and trans-adaptation of the TFPQ into Turkish using the conventional translation back-translation procedure.

Step 2: Linguistic validation of the trans-adapted TFPQ-T's feedback rating.

Step 3: Testing of participants with tinnitus (including those with and without hearing loss) using the trans-adapted questionnaires (TPFQ-T & THI) and calculating test scores.

Step 4: Validation of the TFPQ-T.

Step 5: Evaluation of the validity of the 20-questions TPFQ-T.

TPFQ Turkish version: participants were asked to score each item on a scale of 0 to 100, where 100 is completely agree and 0 is completely disagree. The total score and mean score of each subscale were calculated. The defined subscales are: concentration (questions 3, 7, 11, 15 and 19), emotion (questions 1, 4, 8, 10 and 12), hearing (questions 2, 6, 9, 14 and 17) and sleep (questions 5, 13, 16, 18 and 20) (6).

Scoring and Statistical Analysis

- Each TPFQ-T item was rated on a 0-100 scale, where 0= completely disagree and 100= completely agree.
- The total and subscale scores (concentration, emotion, hearing, sleep) were computed.
- Internal consistency was assessed using Cronbach's alpha coefficient.
- Pearson's and Spearman's correlation coefficients were used to examine validity by comparing TPFQ-T with THI Turkish version (THI-T), BDI-Turkish version (BDI-T), BAI-Turkish version (BAI-T), and PSQI Turkish version (PSQI-T) scores.

Tinnitus Handicap Inventory-Turkish version: Three response alternatives (yes: 4 points; sometimes: 2 points; no: 0 points) on the functional, emotional, and catastrophic implications of tinnitus were given to the subjects in the 25-item THI-T. The total of the scores from the 25 items, which ranged from 0 to 100, was used to calculate the overall THI score (12).

Beck Anxiety Inventory-Turkish version: Anxiety was measured using the 21-item BAI-T, which focuses on somatic symptoms. The degree of botheration caused by each symptom throughout the previous week was indicated by the respondents. Ratings for responses varied from 0 (not at all) to 3 (severely) on a 4-point Likert scale (13).

Beck Depression Inventory Turkish Version: This 21-item multiple-choice questionnaire is commonly used to evaluate the degree of depression. Participants were asked to select the statement from a list of options that most accurately reflected how they felt. Every question on the survey received a score between 0 and 3. The overall score, which ranged from 0 to 63, was then calculated by adding the scores of each item. The reported level of depression increased with increasing scores on the questionnaire (14).

Pittsburgh Sleep Quality Index Turkish Version: PSQI aids in assessing a person's sleep quality during the previous month. There are 24 questions in total. Nineteen of these are answered by the individual, and five are answered by their partner or spouse. Subjective sleep quality, sleep latency, length, habitual sleep efficiency, sleep disorders, use of sleep medicine, and daytime dysfunction are the seven subcomponents of sleep quality that are measured by the individual's responses to the scale's 19 items. The PSQI total score spans from 0 to 21 and is calculated by adding seven subscores. Poorer sleep quality is indicated by a higher overall score (15).

Magnitude Estimation: Participants were asked to rate the loudness of their tinnitus on a scale of 0 (very faint) to 10 (very loud).

Statistical Analysis

IBM's SPSS version 22.0 was utilized for statistical analysis (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA). Data were presented as mean ($\bar{X}$), range, and standard deviation as numerical values or percentages.

The internal consistency of TPFQ-T in overall and of the subgroups were studied using Cronbach's coefficient of alpha; and the associations between the TPFQ scores and other measurements were studied using Spearman's and Pearson's rank correlation coefficients.

Results

The demographic data for each of the 103 participants are given in Table 1. The age range of the participants was 18 to 76 years, with an average of 45.28 years. There were 28 female and 75 male participants. The mean duration of tinnitus was 38.54 months. Forty-one of the patients had left-sided tinnitus, 27 had right-sided tinnitus, and 35 had bilateral tinnitus. The mean loudness of tinnitus was 5.66 on a scale of 0 to 10.

Regarding validity-related surveys, the THI-T had a mean score of 49.37 (43.79-54.96), the PSQI-T had a mean score of 7.49 (6.69-8.29), the BDI-T had a mean score of 13.43 (11.32-15.54) and the BAI-T had a mean score of 14.09 (11.83-16.35). The mean score of TPFQ-T was 47.52 (42.36-52.68).

Patients' hearing status was assessed using pure tone audiometry. The pure tone averages, which include the air conduction thresholds at 0.5 kHz, 1 kHz, 2 kHz, and 4 kHz, are given in Table 2.

Reliability

Cronbach's alpha coefficient values higher than 0.67 are generally considered acceptable, while values above 0.80 indicate good reliability, as suggested by Paiva et al. (16) and Sasaki et al. (17). In our study, Cronbach's alpha was 0.88. Cronbach's alpha was also calculated for each of the four subscales (α=0.86 for concentration; α=0.75 for emotion; α=0.72 for hearing; and α=0.67 for sleep). An item-total correlation greater than 0.50 is typically considered a sign of strong internal consistency (8).

High correlations were found between the total TPFQ-T score and the subscale scores. The strongest correlation was found with the Concentration subscale (0.869), followed by the emotion (0.756), hearing (0.723), and sleep (0.672) subscales. Additionally, inter-item correlations indicated that all subscales were significantly related to the total TPFQ-T score. Specifically, the correlations of concentration, emotion, hearing, and sleep with the total score were 0.930, 0.857, 0.849, and 0.828, respectively. These findings suggest that each subscale substantially contributes to the overall TPFQ-T structure. Table 3 shows the mean scores for the four subscales and the total score of the 20-item TPFQ-T.

Table 1. Characteristics of tinnitus patients (n=103)

Parameter	Values
Age, year	45.28±14.35
Male sex, n (%)	75 (72.8)
Female sex, n (%)	28 (27.2)
Tinnitus duration, months	38.54
Tinnitus side, n (%)	
Left	41 (39.8)
Right	27 (26.2)
Bilateral	35 (34)
Loudness of tinnitus, dB	5.66 (5.17-6.14)
TPFQ-T, mean (95% CI)	47.52 (42.36-52.68)
THI-T, mean (95% CI)	49.37 (43.79-54.96)
PSQI-T, mean (95% CI)	7.49 (6.69-8.29)
BDI-T, mean (95% CI)	13.43 (11.32-15.54)
BAI-T, mean (95% CI)	14.09 (11.83-16.35)

n: Total number of participants, CI: Confidence interval, dB: Decibel, TPFQ-T: Tinnitus Primary Function Questionnaire Turkish version, THI-T: Tinnitus Handicap Inventory Turkish version, PSQI-T: Pittsburgh Sleep Quality Index Turkish version, BDI-T: Beck Depression Inventory Turkish version, BAI-T: Beck Anxiety Inventory Turkish version

Table 2. Hearing status of tinnitus patients

Pure tone audiometry test		Right ear (n=103)	Left ear (n=103)
PTA (0.5, 1, 2, 4 kHz) dB		22.04±18.75	21.66±15.33
Stimulus Frequency			
	0.5 kHz, dB	17.62±18.97	16.34±13.94
	1 kHz, dB	17.56±18.86	15.24±14.11
	2 kHz, dB	18.53±19.10	18.17±16.76
	4 kHz, dB	34.45±27.39	36.89±24.64

n: Total number of participants, PTA: Pure tone average, kHz: Kilohertz, dB: Decibel

Construct Validity

The TPFQ-T's construct validity measures were determined by calculating the Pearson's correlation coefficient values between the test's total score and each of its four subcategory scores, as well as the scores obtained from the four validity test measures (THI-T, BDI-T, BAI-T, and PSQI-T) (Table 4).

The Turkish version of the questionnaire can be found in the Appendix (Appendix 1).

Discussion

Our study aimed to assess the validity and reliability of TPFQ-T. The internal consistency of TPFQ-T was high among the items. There was a correlation between the total items of the TPFQ-T and its subcategories and those of questionnaires measuring comparable parameters. Our findings showed TPFQ-T to be valid and reliable.

Table 3. Mean and standard deviation of total and subscales for TPFQ-T

Patients		**Value**
(n=103)		(mean±SD)
TPFQ-T	Total	47.52±26.39
	Concentration	44.25±29.65
	Emotion	59.71±27.46
	Hearing	41.52±31.28
	Sleep	44.61±33.68

n: Total number of participants, SD: Standard deviation, TPFQ-T: Tinnitus primary function questionnaire Turkish version

According to Tyler et al. (6), tinnitus affects a person's ability to concentrate, feel emotions, hear, and sleep, all of which are important in daily life, work, and social relations. The TPFQ-T yields data on the respective contributions of each subcategory (emotion, concentration, hearing, and sleep measures) to overall severity.

The results of the validation assessment of the TPFQ-T were found comparable to those of the original TPFQ (6). Cronbach's alpha rating for reliability was 0.88 for the Turkish version and 0.92 for the original TPFQ.

The overall score and the subcategory scores of the original TPFQ and K-TPFQ showed a strong correlation with the results obtained from surveys measuring comparable parameters in validity assessments (6,8). For the original TPFQ, the range of Spearman's correlation coefficient values was 0.52 to 0.77, while for TPFQ-T, it was 0.36 to 0.80. Overall, these findings show that TPFQ-T is just as valid and reliable as the original TPFQ.

Nevertheless, there are some limitations to our study, despite the demonstrated validity and reliability of the TPFQ-T. Firstly, TPFQ-T's test-retest reliability was not assessed. Test-retest assessment of the questionnaire measures would increase the reliability of the TPFQ-T by revealing the reliability of participants' responses. On the other hand, the fact that the TPFQ-T results showed a correlation with the results of similar questionnaires suggests that the individuals' answers were consistent.

In the initial TPFQ study, Tyler et al. (6) used the Tinnitus Handicap Questionnaire (THQ), whereas in our study we used THI-T which is widely used in Türkiye. The correlation

Table 4. Correlations between the four questionnaires and the TPFQ-T's total and subscale scores (n=103)

Variables	**THI-T**	**BDI-T**	**BAI-T**	**PSQI-T**
Total scores				
r	0.806*	0.427*	0.369*	0.595*
p	0.000**	0.000**	0.000**	0.000**
Concentration scores				
r	0.805*	0.391*	0.325*	0.525*
p	0.000**	0.000**	0.001**	0.000**
Emotion scores				
r	0.739*	0.390*	0.368*	0.515*
p	0.000**	0.000**	0.000**	0.000**
Hearing scores				
r	0.618*	0.294*	0.278*	0.448*
p	0.000**	0.003**	0.004**	0.000**
Sleep scores				
r	0.653*	0.416*	0.321*	0.606*
p	0.000**	0.000**	0.001**	0.000**

*r: correlation coefficient, **p<0.05, n: Total number of participants, THI-T: Tinnitus Handicap Inventory Turkish version, BDI-T: Beck Depression Inventory Turkish version, BAI-T: Beck Anxiety Inventory Turkish version, PSQI-T: Pittsburgh Sleep Quality Index Turkish version

between the TPFQ-T and THI-T was 0.80, i.e., similar to the corresponding figure of 0.77 between TPFQ and THQ reported in Tyler et al.'s (6) paper.

The tinnitus questionnaires (especially THQ) have also been used for decades to assess treatment-related changes in drugs, devices, cochlear implants, and vagal nerve stimulation (18-21). Therefore, the TPFQ, which is scored between 0 and 100, may also be suitable for use in this field, as it is more likely to detect minor variations.

Conclusion

Any tools or methods used to evaluate psychometric traits and tinnitus severity ought to maintain a high level of accuracy and reliability. A test's validity is determined by its reliability. When used with adult tinnitus sufferers, the TPFQ-T-a cross-cultural adaptation and Turkish translation of the TPFQ-is a viable and trustworthy tool.

We propose that this scale can be employed in Turkish tinnitus studies and clinical practice as a substitute for the current tinnitus scales. To validate the scale as an outcome measure, more research is required.

Ethics

Ethics Committee Approval: The study received ethical approval from the Health Sciences University Non-Interventional Research Ethics Committee (decision no: 19/222, dated: 28/05/2019).

Informed Consent: Written informed consent was taken from all the of the patients.

Footnotes

Authorship Contributions

Concept: F.C.A.Ö., R.T., B.S., Design: F.C.A.Ö., R.T., B.S., Data Collection and/or Processing: F.C.A.Ö., H.K.B., C.E.Ü., Analysis and/or Interpretation: F.C.A.Ö., H.K.B., C.E.Ü., Literature Search: F.C.A.Ö., H.K.B., C.E.Ü., B.S., Writing: F.C.A.Ö., H.K.B.

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

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Main Points

- Tinnitus is a common medical symptom that can be debilitating.
- Currently, there is no objective way to define the presence of tinnitus. Questionnaires are important because they are based on patient self-report.
- Satisfactory values were found for the internal consistency for the Tinnitus Primary Function Questionnaire-Turkish version (TPFQ-T) and the subscales.
- Construct validity was proven for the TPFQ-T and its subscales.

References

1. Vanneste S, To WT, De Ridder D. The psychometric properties of the tinnitus handicap questionnaire in a Dutch-speaking population. Clin Otolaryngol. 2011; 36: 9-16. [Crossref]
2. Xin Y, Tyler R, Yao Z-M, Zhou N, Xiong S, Tao L-Y, et al Tinnitus assessment: Chinese version of the tinnitus primary function questionnaire. World J Otorhinolaryngol Head Neck Surg. 2023; 9: 27-34. [Crossref]
3. Eggermont JJ. The Neuroscience of tinnitus. Oxford University Press; 2012. p. ix. [Crossref]
4. Aksoy S, Firat Y, Alpar R. The tinnitus handicap inventory: a study of validity and reliability. Int Tinnitus J. 2007; 13: 94-8. [Crossref]
5. Caglar O, Guclu O, Oymak S, Derekoy F. Reliability and usability of the Turkish Tinnitus Functional Index. B-ENT. 2019; 15: 303-9. [Crossref]
6. Tyler R, Ji H, Perreau A, Witt S, Noble W, Coelho C. Development and validation of the tinnitus primary function questionnaire. Am J Audiol. 2014; 23: 260-72. [Crossref]
7. Lu T, Liu JH, Li G, Xiang T, Ma Y, Zhong J, et al. Reliability and validity of the Mandarin version of the tinnitus primary function questionnaire: a preliminary observational study. Medicine (Baltimore). 2019; 98: 16104. [Crossref]
8. Shin J, Heo S, Lee HK, Tyler R, Jin IK. Reliability and validity of a Korean version of the tinnitus primary function questionnaire. Am J Audiol. 2019; 28: 362-8. [Crossref]
9. Talaat HS, Ali RH, Zein El Abedein AM. Trans-adaptation and standardization of Arabic version of Tinnitus Primary Function Questionnaire. EJENTAS. 2020; 21: 51-5. [Crossref]
10. Coradini PP, Gonçalves SN, Oiticica J. Translation and validation of the tinnitus primary function questionnaire into Brazilian Portuguese. Braz J Otorhinolaryngol. 2022; 88 (Suppl 3): S109-16. [Crossref]
11. Prochaska JO, DiClemente CC. The transtheoretical approach. Norcross JC, Goldfried MR, editors. Handbook of psychotherapy integration. Oxford University Press; 2005. p. 147-71. [Crossref]
12. Newman CW, Jacobson GP, Spitzer JB. Development of the tinnitus handicap inventory. Arch Otolaryngol Head Neck Surg. 1996; 122: 143-8. [Crossref]
13. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol. 1988; 56: 893-7. [Crossref]
14. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961; 4: 561-71. [Crossref]
15. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989; 28: 193-213. [Crossref]

16. Paiva PC, de Paiva HN, de Oliveira Filho PM, Lamounier JA, Ferreira e Ferreira E, et al. Development and validation of a social capital questionnaire for adolescent students (SCQ-AS). PLoS One. 2014; 9: 103785. [Crossref]
17. Sasaki N, Imamura K, Thuy TTT, Watanabe K, Huong NT, Kuribayashi K, et al. Validation of the job content questionnaire among hospital nurses in Vietnam. J Occup Health. 2020; 62: 12086. [Crossref]
18. Coelho C, Witt SA, Ji H, Hansen MR, Gantz B, et al. Zinc to treat tinnitus in the elderly: a randomized placebo controlled crossover trial. Otol Neurotol. 2013; 34: 1146-54. [Crossref]
19. Dobie RA, Sullivan MD, Katon WJ, Sakai CS, Russo J. Antidepressant treatment of tinnitus patients. Interim report of a randomized clinical trial. Acta Otolaryngol. 1992; 112: 242-7. [Crossref]
20. Pan T, Tyler RS, Ji H, Coelho C, Gehringer AK, Gogel SA. Changes in the tinnitus handicap questionnaire after cochlear implantation. Am J Audiol. 2009; 18: 144-51. [Crossref]
21. De Ridder D, Vanneste S, Engineer ND, Kilgard MP. Safety and efficacy of vagus nerve stimulation paired with tones for the treatment of tinnitus: a case series. Neuromodulation. 2014; 17: 170-9. [Crossref]

Appendix 1. (Turkish Version of the Questionnaire)

Iowa Tinnitus (Kulak Çınlaması) Primer Fonksiyon Anketi (6)

İsim: Tarih:

Lütfen her bir madde için 0'dan (hiç katılmıyorum) 100'e (tamamen katılıyorum) kadar olan ölçek üzerinden puanlama yapınız.

#	Açıklama	0-100
1	Kulak çınlaması yüzünden bazı önemli görevlerde dikkatimi toplamakta zorluk çekiyorum.	
2	Kulak çınlamam yüzünden geceleri uyanık şekilde uzanıyorum.	
3	Kulak çınlamamın gitmesini istiyorum. Çok sinir bozucu oluyor.	
4	Kulak çınlamam yüzünden geceleri uyumakta zorluk çekiyorum.	
5	Aynı anda bir sürü şey olurken, kulak çınlamam en önemli olanıyla ilgilenmeme engel oluyor.	
6	Kulak çınlamam bazı konuşma seslerini engelliyor.	
7	Bir şeyler hakkında rahat düşünememem kulak çınlamamın en kötü etkilerinden birisidir.	
8	Kulak çınlamam can sıkıcıdır.	
9	Kulak çınlamam hakkındaki en kötü şeylerden birisi konuşmayı anlamama olan etkisidir, işitme kaybımın herhangi bir etkisinden fazla ve ötesindedir.	
10	Kulak çınlamam işitme kaybımdan bağımsız olarak müzik ve şarkılardan zevk almama engel oluyor.	
11	Gün boyunca yorgun oluyorum çünkü kulak çınlamam uykumu bölüyor.	
12	İşitme kaybıma ek olarak, kulak çınlamam konuşmayı anlamama engel oluyor.	
13	Kulak çınlamam yüzünden bunalımdayım.	
14	Geceleri uyandığımda, kulak çınlamam tekrar uykuya dalmamı güçleştiriyor.	
15	İç huzurumun bozulması kulak çınlamamın en kötü etkilerinden birisidir.	
16	Sessiz bir odada okuma yaparken kulak çınlamam yüzünden dikkatimi toplamakta sorun yaşıyorum.	
17	Uyumamdaki güçlük kulak çınlamamın en kötü etkilerinden birisidir.	
18	Kulak çınlamam yüzünden endişeliyim.	
19	Kulak çınlamamın işitmemdeki etkisi işitme kaybımın etkisinden daha kötüdür.	
20	Kulak çınlamam bazı görevlerin üzerinde odaklanmamı zorlaştırıyormuş gibi hissediyorum.	

Evaluation of the Early Radioprotective Effect of Curcumin on the Rat Larynx

Original Investigation

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Abstract

Objective: The aim of this study was to investigate whether the side effects of radiotherapy (RT) could be reduced by curcumin administered to rats receiving RT to the larynx.

Methods: Forty male Wistar Albino rats were randomly and equally divided into four groups: RT only (Group I), RT+curcumin+dimethyl sulfoxide (Group II), RT+dimethyl sulfoxide (Group III), and curcumin+dimethyl sulfoxide (Group IV). Curcumin was administered intraperitoneally, dissolved in dimethyl sulfoxide, starting five days before RT. A single 16 Gy dose of X-ray was applied to the neck region in groups receiving RT. All groups were sacrificed on the third day after RT. Laryngeal tissues were excised and analyzed histopathologically (for edema, hyperemia, pseudostratification, necrosis, cilia loss, and inflammation) and immunohistochemically [Tumor Necrosis Factor-alpha (TNF-α) expression]. Histopathological parameters were graded as none, mild, moderate, and severe (0, 1+, 2+, 3+). The severity of TNF-α expression was scored between 0 and 3.

Results: The formation of edema, hyperemia, necrosis, and pseudostratification in Group II rats was statistically significantly reduced (p=0.001, 0.003, 0.004, and 0.005, respectively). Similarly, TNF-α expression was also significantly decreased in Group II rats (p=0.009). However, no statistically significant differences were observed for cilia loss and inflammation (p=0.055 and 0.091, respectively).

Conclusion: Our findings suggest that curcumin may reduce the development of edema, hyperemia, necrosis, and pseudostratification in laryngeal tissue due to RT. While further research is needed to determine whether curcumin confers protection against RT-induced damage in tumor tissues, the results of this study suggest that curcumin, a natural, non-toxic, and cost-effective dietary compound, has the potential to be used as a radioprotective agent.

Keywords: Larynx, curcumin, radiotherapy, radiation protection, antioxidants, tumor necrosis factor-alpha, inflammation

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Introduction

Laryngeal cancers (LCs) rank second among head and neck malignancies after oral cavity cancers, excluding skin cancer (1). Radiotherapy (RT) for LCs is used for primary (definitive), adjuvant, palliative, and salvage purposes. Primary RT is particularly beneficial for patients with early-stage LC, those who do not accept surgical treatment, and inoperable cases (2). Adjuvant RT is administered to all T3-T4 stage laryngeal tumors, as well as to those with neck lymph node involvement, extracapsular extension, or histopathologically positive surgical margins (2,3). Clinical side effects of RT in patients with LC include laryngeal edema, impairment of vocal function, dysphonia, dysphagia, aspiration, and chondronecrosis (4,5).

To reduce the secondary morbidity of RT, healthy non-cancerous cells in laryngeal tissue should be preserved as much as possible. Various methods have been developed to reduce or eliminate the adverse effects of RT on laryngeal tissue and its associated pathologies. One of the most used methods is the systemic administration of radioprotective agents. Amifostine, a widely used radioprotective agent, has been approved for clinical use by the U.S. Food and Drug Administration. However, due to adverse effects such as hypotension and allergic reactions, the use of amifostine is limited (6). Therefore, natural, non-toxic radioprotective substances with a long half-life and minimal side effects are being investigated. The radioprotective activity of curcumin (CUR) has been widely studied, and its protective effects have been reported in numerous rat studies (7,8).

CUR (diferuloylmethane) is a bioactive compound with the chemical formula $C_{21}H_{20}O_6$, which gives turmeric its characteristic yellow color. It is extracted from the rhizomes of the Curcuma longa plant. CUR exhibits various biological effects, including antioxidant, anti-inflammatory, anti-angiogenic, chemoprotective, chemosensitizing, radioprotective, and radiosensitizing properties (9-11). Regarding the underlying mechanisms of CUR's potential therapeutic effects, it inhibits cell membrane lipid peroxidation, thereby reducing the formation of free radicals. Moreover, it has been shown to interact with several signal transduction molecules, including mitogen-activated protein kinases, Janus kinase/signal transducer and activator of transcription, and nuclear factor-kappa B (NF-κB). As a result of these interactions, CUR can reduce pro-inflammatory cytokines, such as interleukin-1 (IL-1), IL-8, Tumor Necrosis Factor-alpha (TNF-α), and interferon-gamma (12).

Dimethyl sulfoxide (DMSO) is a widely used chemical solvent and a free radical scavenger. It has been observed to exhibit analgesic, anti-inflammatory, radioprotective, and chemoprotective properties (13). In laboratory settings, water-insoluble therapeutic and toxic substances are commonly dissolved in DMSO (14). According to the manufacturer's specifications, the CUR powder used in this study is soluble in DMSO (15).

The objective of this study was to determine whether the adverse side effects of RT could be mitigated by administering CUR to rats receiving RT to the larynx.

Methods

Ethical Approval and Experimental Groups

Ethical approval for this study was obtained from the Burdur Mehmet Akif Ersoy University (MAKU) Animal Experiments Local Ethics Committee (date: 20.05.2021, number: 773). A total of 40 male Wistar Albino rats (250±20 g) were procured from the Burdur MAKU Laboratory Animals Production and Experimental Research Center. After a one-week acclimatization period, the rats were randomly assigned to four equal groups:

- Group I: Received only RT
- Group II: Received RT+CUR+DMSO
- Group III: Received RT+DMSO
- Group IV: Received CUR+DMSO

All animals were housed under standard environmental conditions (24 °C, with a 12-hour light-dark cycle) and provided ad libitum access to standard food and fresh water.

Curcumin-Dimethyl Sulfoxide Application

The solubility of CUR powder (C1386, Sigma-Aldrich, Schnelldorf, Germany) in DMSO (Isolab Chemicals, Eschau, Germany) was determined to be 25 mg/mL, as stated in the product catalog. CUR was administered at a dose of 100 mg/kg, with the corresponding DMSO dose calculated as 4 mL/kg based on solubility and the required CUR amount. CUR and DMSO administration in Groups II, III, and IV commenced five days before RT and was continued once daily via intraperitoneal (IP) injection (16).

Radiotherapy Application

For RT application, all rats in Groups I, II, and III were first sedated with xylazine (10 mg/kg, Rompun 2%, Bayer, Leverkusen, Germany) and ketamine (90 mg/kg, Ketasol 10%, Richter Pharma, Wels, Austria) via IP injection. The rats were then immobilized in the supine position, and three-dimensional conformal RT was planned based on computed tomography images of the rat's neck region.

A single dose of 16 Gy RT was administered using 6 MV photon energy, maintaining a source-to-skin distance of 100 cm at a depth of 3 cm, utilizing the Varian DBX (Varian Medical Systems, Palo Alto, CA, USA) device (17,18). Following RT, one rat in Group I died in the second hour, while two rats in Group II died in the fourth and fifth hours,

respectively. On the third day after RT, all remaining rats were sacrificed via IP administration of a ketamine (270 mg/kg) and xylazine (30 mg/kg) mixture.

A necropsy procedure was performed to obtain laryngeal tissue samples, which were immediately fixed in formaldehyde and labeled according to their respective groups (Figure 1).

Histopathological and Immunohistochemical Examinations

Laryngeal samples obtained during necropsy were fixed in 10% neutral formaldehyde solution. After two days of fixation, the samples were longitudinally sectioned and placed into cassettes for routine tissue processing using a fully automated tissue processor (Leica ASP300S; Leica Microsystem, Nussloch, Germany). The processed samples were embedded in paraffin wax, cooled for 4-5 hours, and then serial sections (5 µm thick) were obtained using a Leica 2155 fully automatic rotary microtome (Leica Microsystem, Nussloch, Germany).

The sections were stained with hematoxylin-eosin and cover-slipped for examination under an Olympus CX21 light microscope. Microscopic digital images were captured using an Olympus DP26 camera and transferred to a computer for analysis via the Database Manual Cell Sens Life Science Imaging Software System (Olympus Corporation, Tokyo, Japan).

Histopathological parameters for evaluation included: Edema, hyperemia, pseudostratification, necrosis, ciliary loss, inflammation.These parameters were graded as follows:

None (0)

Mild (1 positive)

Moderate (2 positive)

Severe (3 positive) (Table 1).

Histopathological evaluations were performed by a single pathologist who was blinded to the study groups to eliminate bias. For immunohistochemical analysis, additional sections were mounted on Poly-L-lysine-coated slides and stained for TNF-α expression using the streptavidin-biotin complex peroxidase method. Primary and secondary antibodies from Abcam (UK) were used for this procedure. Immunohistochemical staining for TNF-α [Anti-TNF alpha antibody (EPR21753-109) (ab205587), diluted 1:100] was conducted using the UltraVision Detection System Anti-Polyvalent HRP kit (TP-060-HL) (Thermo Shandon Limited, Cheshire, England).

The reaction was visualized using 3,3'-diaminobenzidine chromogen, and negative controls were obtained by incubating sections with antibody dilution solution instead of primary antibodies. Finally, counterstaining was

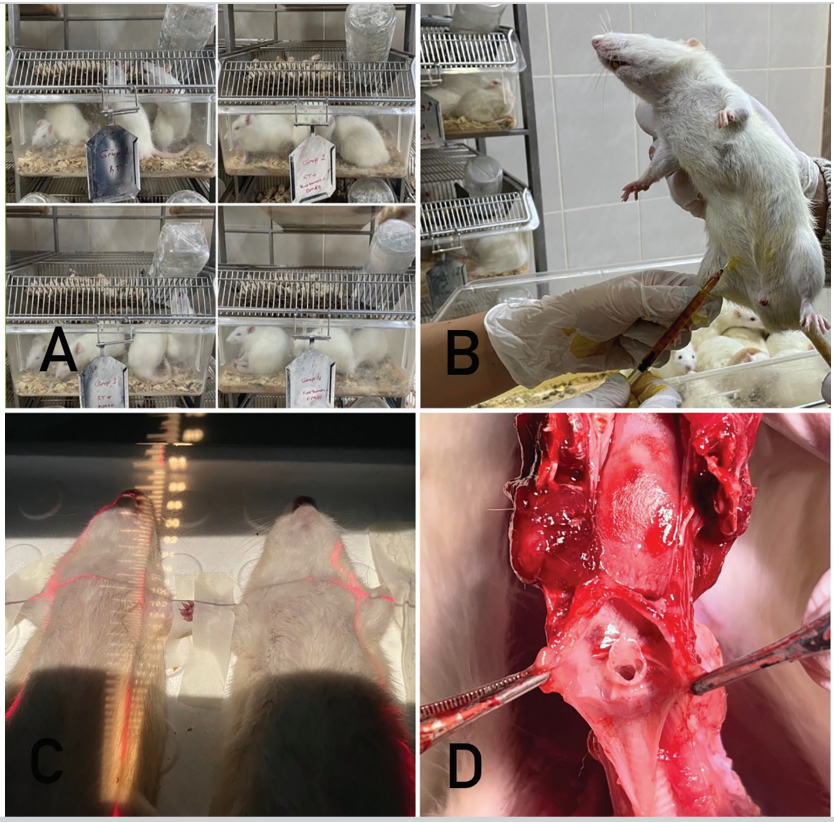

Figure 1. Experimental setup demonstrating the establishment of study groups (A), administration of **curcumin and/or dimethyl sulfoxide (B), irradiation of the neck region (C), and excised laryngeal tissue (D).

Table 1. Histopathological parameters and scoring for laryngeal tissue

Parameters	0 None	1+ Mild	2+ Moderate	3+ Severe
Edema	<25%	26-50%	51-75%	>76%
Hyperemia	<25%	26-50%	51-75%	>76%
Necrosis	None	Single cell necrosis	Necrosis in local area	Diffuse necrosis
Pseudostratification	Normal	Low and mild	Local and moderate	Diffuse and marked
Loss of cilia	None	Mild	Moderate	Severe
Inflammation	1-20 lymphocytes no neutrophils	21-50 lymphocytes 1-2 neutrophils	51-80 lymphocytes 3-10 neutrophils	81-120 lymphocytes >10 neutrophils

performed with Harris hematoxylin, followed by cover-slipping in preparation for light microscopy examination. For immunohistochemical evaluations, 100 cells were counted in five fields under a 40× objective lens per section. Based on the percentage of positively stained cells, the scoring system was as follows:

<25% positive cells (0)

26-50% (1)

51-75% (2)

>76% (3)

Histopathological evaluations were conducted under a 20× objective lens, and scores were calculated based on the parameters in Table 1 using ImageJ 1.46r software (National Institutes of Health, Bethesda, MD).

Statistical Analysis

Data analysis was performed using SPSS 24.0 software (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY, USA). Descriptive findings are presented as frequency (n) and percentage (%) distributions for categorical variables and as median, minimum, and maximum values for continuous variables. Since each group contained fewer than 30 samples, non-parametric statistical methods were applied. The Kruskal-Wallis test was used to compare histopathological and immunohistochemical scores across groups. If a significant difference was found, pairwise comparisons were conducted using the Bonferroni-corrected Mann-Whitney U test. The accepted level of statistical significance was $p<0.05$. Effect size was set at $f=0.75$, with a significance level (α) of 0.05 and statistical power ($1-\beta$) of 0.95. A total sample size of 36 animals was determined to achieve a power of 95.79%, as calculated using the G*Power 3.1.9.4 program (Heinrich-Heine-Universität Düsseldorf, Nordrhein-Westfalen, Germany).

Results

Widespread epithelial shedding and epithelial cell necrosis were observed in the rats in Group I. Epithelial proliferation was noted in various areas, along with the presence of intraepithelial neutrophils and leukocytes in multiple regions. Additionally, marked hyperemia and inflammatory cell infiltration were detected in the lamina propria. Mild cilia loss was observed in some cells.

A marked improvement in all pathological findings was noted in the laryngeal tissues of rats in Group II. Epithelial shedding was significantly reduced, and no proliferative changes were detected in any of the rats in this group. Additionally, cilia structures were significantly preserved. Similarly, a notable reduction in inflammatory cell infiltration was observed in the lamina propria.

A mild reduction in pathological findings was observed in Group III rats. Compared to Group III, rats in Group II exhibited greater protection and preservation, as reflected in their pathological scores. Laryngeal histology appeared normal in Group IV (Figure 2). A comparative analysis of histopathological parameters across all groups is presented in Table 2.

In immunohistochemical examinations, a significant increase in immunoreactivity was observed in all cell types, particularly in epithelial cells of Group I. However, a decrease in expression was noted in Groups II and III, with a more pronounced reduction in Group II. In Group IV, while no expression was detected in most rats, sporadic mild expression was observed in a few cells in some rats (Figure 3). A comparative analysis of immunohistochemical parameters across groups is provided in Table 3.

Discussion

Although RT is a successful treatment for LC, it also has adverse effects on the larynx. These may include alterations in taste perception, mucositis, pain, hyperemia, and tenderness in the irradiated skin area, as well as dysphonia, xerostomia (dry mouth), swallowing and chewing difficulties, nausea, and deterioration in hematological parameters (5,19). In a study examining RT-induced histopathological changes in the larynx, an acute inflammatory reaction characterized by leukocyte infiltration, necrosis, and hemorrhage was observed in the deep connective tissues within 2 to 12 days post-RT, leading to damage in the respiratory epithelium.

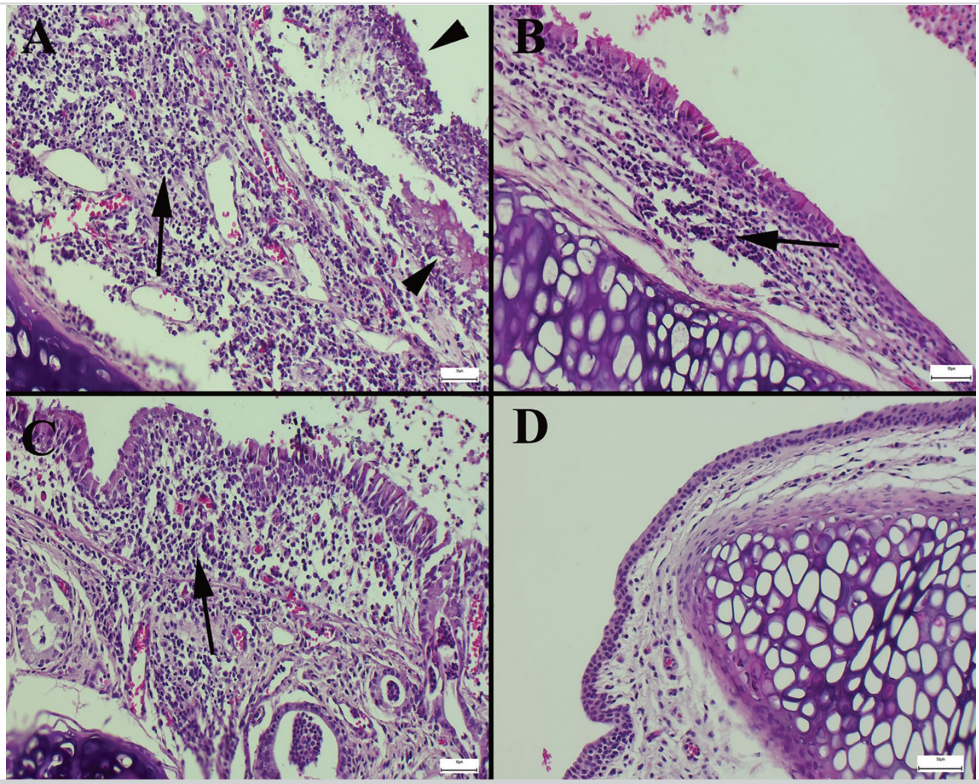

Figure 2. Histopathological comparison of laryngeal tissues across groups. (A) Severe epithelial loss, necrosis (arrowhead), and inflammatory reaction (arrow) in Group I. (B) Marked improvement in the pseudostratified epithelial layer with only mild inflammatory reaction (arrow) in the propria mucosa in Group II. (C) Slight healing of the pseudostratified epithelial layer with a mildly reduced inflammatory reaction (arrow) in Group III. (D) Normal laryngeal epithelial structure in Group IV. Hematoxylin & eosin (HE) staining; scale bar = 50 μm.

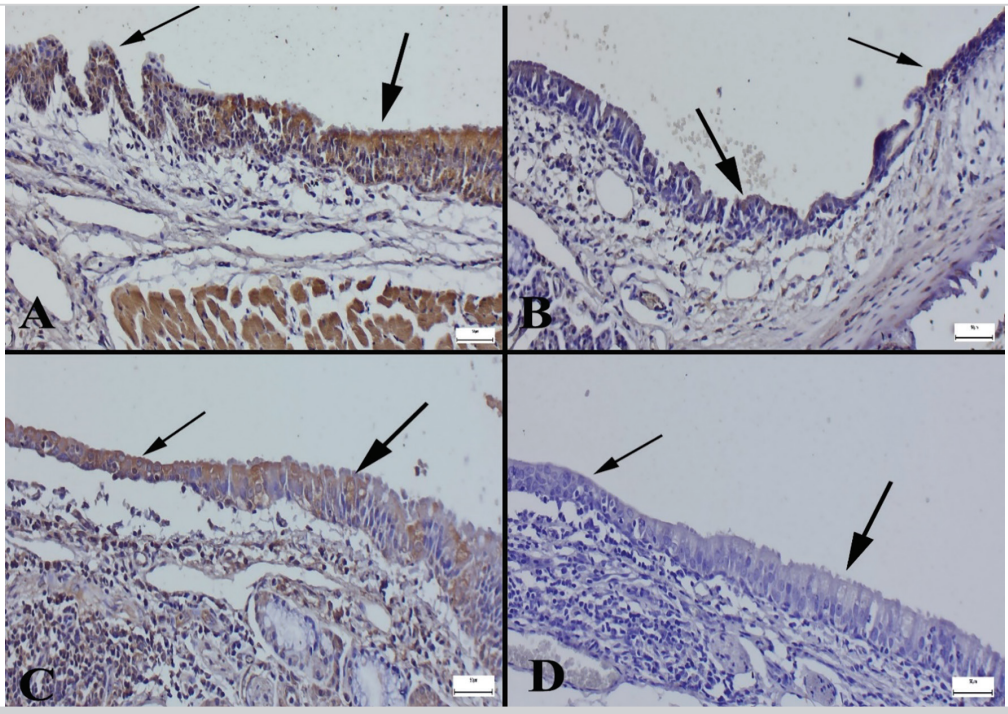

Figure 3. Immunohistochemical analysis of TNF-α expression across groups. (A) Strong TNF-α expression in Group I. (B) Decreased expression in Group II. (C) Slightly reduced expression in Group III. (D) Negative expression in Group IV. Thick arrows indicate the pseudostratified epithelium, while thin arrows denote the stratified squamous epithelium. Streptavidin-biotin peroxidase method; scale bar = 50 μm.

Table 2. Comparison of histopathological values in the groups

		n	Min.	Max.	Median	p-value*	p-value⁺	
Edema	**Group I**	9	2.00	3.00	3.00	<0.001	G1-G2	0.001
							G1-G3	0.091
	Group II	8	0.00	1.00	0.50		**G1-G4**	**<0.001**
							G2-G3	0.695
	Group III	10	1.00	2.00	1.00		**G2-G4**	1.000
							G3-G4	**0.027**
	Group IV	10	0.00	1.00	0.00		-	-
Hyperemia	**Group I**	9	2.00	3.00	3.00	<0.001	**G1-G2**	**0.003**
							G1-G3	0.143
	Group II	8	0.00	1.00	1.00		**G1-G4**	**<0.001**
							G2-G3	1.000
	Group III	10	0.00	2.00	1.50		**G2-G4**	1.000
							G3-G4	**0.031**
	Group IV	10	0.00	1.00	0.00		-	-
Necrosis	**Group I**	9	1.00	2.00	2.00	<0.001	G1-G2	0.004
							G1-G3	0.001
	Group II	8	0.00	1.00	0.00		**G1-G4**	**<0.001**
							G2-G3	1.000
	Group III	10	0.00	1.00	0.00		**G2-G4**	1.000
							G3-G4	1.000
	Group IV	10	0.00	0.00	0.00		-	-
Pseudo stratification	**Group I**	9	1.00	2.00	1.00	<0.001	**G1-G2**	**0.005**
							G1-G3	0.164
	Group II	8	0.00	1.00	0.00		**G1-G4**	**<0.001**
							G2-G3	1.000
	Group III	10	0.00	1.00	1.00		**G2-G4**	1.000
							G3-G4	0.296
	Group IV	10	0.00	1.00	0.00		-	-
Loss of cilia	**Group I**	9	1.00	2.00	1.00	<0.001	**G1-G2**	0.055
							G1-G3	1.000
	Group II	8	0.00	1.00	0.50		**G1-G4**	**<0.001**
							G2-G3	0.455
	Group III	10	0.00	2.00	1.00		**G2-G4**	0.608
							G3-G4	**0.002**
	Group IV	10	0.00	0.00	0.00		-	-
Inflammation	**Group I**	9	1.00	2.00	2.00	0.001	**G1-G2**	0.091
							G1-G3	0.130
	Group II	8	0.00	2.00	0.50		**G1-G4**	**<0.001**
							G2-G3	1.000
	Group III	10	0.00	2.00	1.00		**G2-G4**	0.758
							G3-G4	0.344
	Group IV	10	0.00	1.00	0.00		-	-

The significance value was calculated with Bonferroni correction for multiple comparisons. The significance value was determined as $p<0.05$.

*According to Kruskal-Wallis test, ⁺According to Mann-Whitney U test, n: Number of rats in group, Min.: Minimum, Max.: Maximum

Table 3. Comparison of immunohistochemical values in the groups

TNF-α expression	n	Min.	Max.	Median	p-value*	p-value⁺	
Group I	9	2.00	3.00	3.00	**<0.001**	**G1-G2**	**0.009**
						G1-G3	0.407
						G1-G4	**<0.001**
Group II	8	1.00	2.00	1.00		**G2-G3**	0.845
						G2-G4	0.564
Group III	10	1.00	3.00	2.00		**G3-G4**	**0.005**
Group IV	10	0.00	1.00	0.00		-	-

The significance value was calculated with Bonferroni correction for multiple comparisons. The significance value was determined as p<0.05

*According to Kruskal-Wallis test, ⁺According to Mann-Whitney U test, n: Number of rats in group, Min.: Minimum, Max.: Maximum

Additionally, thinning of small blood vessels and lymphatics resulted in increased endothelial permeability and interstitial edema (20,21).

Radioprotective agents are used to mitigate these complications. Hosseinimehr (22) suggested that an ideal radioprotective agent should effectively shield healthy tissues from RT-induced damage, be easy to administer, exhibit low toxicity, and be compatible with other medications taken by the patient. CUR, whose radioprotective properties have been widely reported, is a phytochemical with anticancer, anti-inflammatory, and antioxidant activities, historically used in traditional medicine (23,24).

In a study conducted by Lopez-Jornet et al. (25) in rats, a single dose of lycopene (20 mg/kg) and CUR (50 mg/kg) was dissolved in DMSO and administered IP'ly 24 hours before RT. Histopathological examination revealed that rats receiving lycopene and CUR exhibited reduced cell necrosis, structural damage, vacuolization, and acinar duct loss in the parotid glands following 20 Gy RT to the neck region.

While numerous studies have investigated the radioprotective efficacy of CUR in RT-treated rats, none have examined its effectiveness in laryngeal tissues. Therefore, our study aimed to evaluate the potential radioprotective effects of CUR on the rat larynx. In a study by Jagetia and Rajanikant (26), CUR doses of 25, 50, 100, 150, and 200 mg/kg were tested, and the maximum recovery rate was observed in rats receiving 100 mg/kg. Based on these findings, we selected a 100 mg/kg dose of CUR for our study. Additionally, due to CUR's low oral bioavailability, IP administration was preferred to standardize the delivered dose (10). Considering previous studies, sacrifice was scheduled for the third day after RT (25,27,28). A longer observation period could have allowed for compensatory antioxidant mechanisms, potentially masking the effects of CUR. Thus, sacrifice on day 3 was deemed appropriate.

In a study conducted by Chen et al. (29), IP'ly administered CUR significantly reduced brain edema in rats subjected to traumatic brain injury. Similarly, in our study, RT-induced edema in the larynx was significantly reduced in rats receiving CUR+DMSO, with a statistically significant difference between Groups I and II (p=0.001). Memis et al. (30) reported that CUR administration in rats with experimental sepsis reduced edema, inflammation, and hyperemia, as observed in histopathological examinations. Consistently, in our study, hyperemia was significantly reduced in Group II (p=0.003). Conversely, in an *in vitro* study by Ghoneim (31), CUR was not found to protect against ethanol-induced cell necrosis in rat hepatocytes. In contrast, in our study, RT-induced necrosis was significantly less common in the laryngeal tissues of Groups II and III, with statistically significant differences between Groups I-II and I-III (p=0.004 and p=0.001, respectively). RT-induced necrosis was observed at a moderate level in Group I, while CUR appeared to mitigate laryngeal necrosis, suggesting a protective effect. This result differs from some reports in the literature, possibly due to the increased epithelial damage associated with administering RT as a single dose rather than fractionally.

Pseudostratification due to RT was mild in our study. Comparisons of the pseudostratification parameter revealed that CUR+DMSO administration reduced this feature, with a statistically significant difference between Groups I and II (p=0.005).

In a study by Oyan et al. (27), pseudostratification following RT was found to be at a level comparable to the control group, while mild cilia loss was reported in laryngeal tissue. In our study, no statistically significant difference was observed between Groups I and II in cilia loss (p=0.055). Justo et al. (32) demonstrated that CUR suppressed TNF-α release and reduced inflammation in rats with apical periodontitis. However, in our study, comparisons between Groups I-II and Groups I-III for inflammation were not statistically significant (p=0.091, p=0.130, respectively). Although CUR+DMSO and DMSO-alone administration did not result in statistically significant reductions in RT-induced inflammation, the lower

median values in Groups II and III compared to Group I suggest some degree of radioprotective efficacy.

TNF-α is a pro-inflammatory cytokine produced by lymphocytes, neutrophils, monocytes, and other immune cells during acute inflammation. It plays a key role in signaling pathways leading to necrosis and apoptosis (33). A significant increase in serum TNF-α levels was observed in patients receiving RT to the head and neck region, with X-rays inducing TNF-α release, leading to synergistic and distant cytotoxic effects (34). Another study reported elevated levels of NF-κB and growth factors, such as vascular endothelial growth factor, matrix metalloproteinases, IL-6, and IL-8, following RT and chemotherapy. It has been suggested that TNF-α plays a key role in the development of radioresistance and chemoresistance in oral cavity cancers (35). Therefore, inhibiting NF-κB may enhance the efficacy of RT and chemotherapy. In a study by Li et al. (36), CUR reduced TNF-α levels, alleviating diabetes-related allodynia and hyperalgesia in rats with experimental diabetes. In our study, TNF-α expression was significantly lower in Group II compared to Group I (p=0.009).

Yang et al. (37) demonstrated that DMSO reduced acute radiation-induced damage in the oral mucosa of rats. In our study, necrosis was significantly reduced in Group III compared to Group I (p=0.001). While partial improvements were observed in edema, hyperemia, cilia loss, inflammation, pseudostratification, and TNF-α expression, these differences were not statistically significant.

We acknowledge several limitations in our study. First, we only examined the acute effects of RT, excluding chronic period effects. Second, we did not measure oxidative and non-oxidative blood enzyme levels involved in pathological changes. Third, CUR and DMSO blood concentrations were not measured. Finally, the animal model used did not include laryngeal tumors, which may exhibit different responses to RT and CUR treatment.

Conclusion

Our findings suggest that CUR may reduce RT-induced edema, hyperemia, necrosis, and pseudostratification in laryngeal tissue, indicating potential radioprotective effects. Therefore, we conclude that CUR could serve as an effective radioprotective agent. Future studies should investigate CUR's protective effects on tumor tissues exposed to RT. We believe that our study is promising, as it highlights CUR-a food-derived, natural, non-toxic, and cost-effective compound-as a potential radioprotective agent.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Burdur Mehmet Akif Ersoy University (MAKU) Animal Experiments Local Ethics Committee (date: 20.05.2021, number: 773).

Informed Consent: Since this study was conducted on animals, patient consent was not required.

Footnotes

Authorship Contributions

Surgical and Medical Practices: F.C., Y.Ç.K., H.Y., E.O., Concept: F.C., Y.Ç.K., Ö.Ö., H.Y., E.O., M.E.S., Design: F.C., Y.Ç.K., H.Y., E.O., M.E.S., Data Collection and/or Processing: E.E.Ö., Analysis and/or Interpretation: F.C., Y.Ç.K., Ö.Ö., E.E.Ö., E.O., M.E.S., Literature Search: F.C., Y.Ç.K., Ö.Ö., E.E.Ö., M.E.S., Writing: F.C.

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

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Main Points

- Laryngeal cancers rank second among head and neck malignancies, following oral cavity cancers, excluding skin cancer.
- Radiotherapy (RT) for laryngeal cancer has been associated with clinical side effects, including laryngeal edema, vocal function impairment, dysphonia, dysphagia, aspiration, and chondronecrosis.
- Curcumin demonstrated radioprotective effects by preventing RT-induced edema, hyperemia, necrosis, and pseudostratification in laryngeal tissue, while also reducing TNF-α expression levels.
- This experimental study provides promising evidence that curcumin, a food-derived, natural, non-toxic, and cost-effective compound, may serve as a radioprotective agent. Our findings may contribute to guiding future research in this field.

References

1. Başaran B, Polat B, Ulusan M, Aslan İ. Gastroesophageal reflux disease: is it a causative factor in laryngeal cancer? J Ist Faculty Med. 2011; 74: 55-58. [Crosref]
2. Şen M, Karakaya E, Demiral AN. Baş Boyun Kanserinde Radyoterapi. In: Kulak Burun Boğaz Hastalıkları ve Baş-Boyun Cerrahisi. Koç C, Editor. 3rd ed. Ankara: Güneş Tıp Kitabevi. 2019. p. 1053-75. [Crosref]
3. Myers EN, Fagan JF. Management of the neck in cancer of the larynx. Ann Otol Rhinol Laryngol. 1999; 108: 828-32. [Crosref]
4. Barnhart MK, Hutchison AR. Perspectives on optimizing radiotherapy dose to the dysphagia/aspiration-related structures for patients with head and neck cancer. Curr Opin Otolaryngol Head Neck Surg. 2019; 27: 157-61. [Crosref]

5. Rancati T, Schwarz M, Allen AM, Feng F, Popovtzer A, Mittal B, et al. Radiation dose-volume effects in the larynx and pharynx. Int J Radiat Oncol Biol Phys. 2010; 7: S64-9. [Crosref]
6. Schuchter LM. Guidelines for the administration of amifostine. Semin Oncol. 1996;23:40-3. [Crosref]
7. Kolivand S, Amini P, Saffar H, Rezapoor S, Motevaseli E, Najafi M, et al. Evaluating the Radioprotective Effect of Curcumin on Rat's Heart Tissues. Curr Radiopharm. 2019; 12: 23-8. [Crosref]
8. Cho YJ, Yi CO, Jeon BT, Jeong YY, Kang GM, Lee JE, et al. Curcumin attenuates radiation-induced inflammation and fibrosis in rat lungs. Korean J Physiol Pharmacol. 2013; 17: 267-74. [Crosref]
9. Scartezzini P, Speroni E. Review on some plants of Indian traditional medicine with antioxidant activity. J Ethnopharmacol. 2000;71:23-43. [Crosref]
10. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. Mol Pharm. 2007; 4: 807-18. [Crosref]
11. Jagetia GC. Radioprotection and radiosensitization by curcumin. Adv Exp Med Biol. 2007; 595: 301-20. [Crosref]
12. Sreejayan N, Rao MN. Free radical scavenging activity of curcuminoids. Arzneimittelforschung. 1996; 46: 169-71. [Crosref]
13. Brayton CF. Dimethyl sulfoxide (DMSO): a review. Cornell Vet. 1986; 76: 61-90. [Crosref]
14. Swanson BN. Medical use of dimethyl sulfoxide (DMSO). Rev Clin Basic Pharm. 1985; 5: 1-33. [Crosref]
15. Sigma-Aldrich. Accessed 22.05.2021. https://www.sigmaaldrich.com/TR/en/product/sigma/c1386. [Crosref]
16. Okunieff P, Xu J, Hu D, Liu W, Zhang L, Morrow G, et al. Curcumin protects against radiation-induced acute and chronic cutaneous toxicity in mice and decreases mRNA expression of inflammatory and fibrogenic cytokines. Int J Radiat Oncol Biol Phys. 2006; 65: 890-8. [Crosref]
17. Aras S, Efendioğlu M, Wulamujiang A, Ozkanli SS, Keleş MS, Tanzer İO. Radioprotective effect of melatonin against radiotherapy-induced cerebral cortex and cerebellum damage in rat. Int J Radiat Biol. 2021; 97: 348-55. [Crosref]
18. Aitasalo K, Aro HT, Virolainen P, Virolainen E. Healing of microvascular free skin flaps in irradiated recipient tissue beds. Am J Surg. 1992; 164: 662-6. [Crosref]
19. Barnhart MK, Hutchison AR. Perspectives on optimizing radiotherapy dose to the dysphagia/aspiration-related structures for patients with head and neck cancer. Curr Opin Otolaryngol Head Neck Surg. 2019; 27: 157-61. [Crosref]
20. Ward PH, Calcaterra TC, Kagan AR. The enigma of post-radiation edema and recurrent or residual carcinoma of the larynx. Laryngoscope. 1975;85:522-9. [Crosref]
21. Calcaterra TC, Stern F, Ward PH. Dilemma of delayed radiation injury of the larynx. Ann Otol Rhinol Laryngol. 1972; 81: 501-7. [Crosref]
22. Hosseinimehr SJ. Trends in the development of radioprotective agents. Drug Discov Today. 2007; 12: 794-805.
23. Liu C, Rokavec M, Huang Z, Hermeking H. Curcumin activates a ROS/KEAP1/NRF2/miR-34a/b/c cascade to suppress colorectal cancer metastasis. Cell Death Differ. 2023; 30: 1771-85. [Crosref]
24. Su LQ, Wang YD, Chi HY. Effect of curcumin on glucose and lipid metabolism, FFAs and TNF-α in serum of type 2 diabetes mellitus rat models. Saudi J Biol Sci. 2017; 24: 1776-80. [Crosref]
25. Lopez-Jornet P, Gómez-García F, García Carrillo N, Valle-Rodríguez E, Xerafin A, Vicente-Ortega V. Radioprotective effects of lycopene and curcumin during local irradiation of parotid glands in Sprague Dawley rats. Br J Oral Maxillofac Surg. 2016; 54: 275-9. [Crosref]
26. Jagetia GC, Rajanikant GK. Effect of curcumin on radiation-impaired healing of excisional wounds in mice. J Wound Care. 2004; 13: 107-9. [Crosref]
27. Oyan S, Tatlıpınar A, Atasoy BM, Güneş P, Özbeyli D, Keskin S, et al. Early effects of irradiation on laryngeal mucosa in a gastroesophageal reflux model: an experimental study. Eur Arch Otorhinolaryngol. 2018; 275: 2089-94. [Crosref]
28. Lidegran M, Forsgren S, Dahlqvist A, Franzén L, Domeij S. Short- and long-term effects of irradiation on laryngeal mucosa of the rat. Acta Oncol. 1999; 38: 1081-91. [Crosref]
29. Chen B, Shi QX, Nie C, Zhao ZP, Wang T, Zhou Q, et al. Curcumin alleviates oxidative stress, neuroinflammation, and promotes behavioral recovery after traumatic brain injury. Curr Neurovasc Res. 2023; 20: 43-53. [Crosref]
30. Memis D, Hekimoglu S, Sezer A, Altaner S, Sut N, Usta U. Curcumin attenuates the organ dysfunction caused by endotoxemia in the rat. Nutrition. 2008; 24: 1133-8. [Crosref]
31. Ghoneim AI. Effects of curcumin on ethanol-induced hepatocyte necrosis and apoptosis: implication of lipid peroxidation and cytochrome c. Naunyn Schmiedebergs Arch Pharmacol. 2009; 379: 47-60. [Crosref]
32. Justo MP, Cardoso CBM, Cantiga-Silva C, de Oliveira PHC, Sivieri-Araújo G, Azuma MM, et al. Curcumin reduces inflammation in rat apical periodontitis. Int Endod J. 2022; 55: 1241-51. [Crosref]
33. Comert S, Sen S, Eryilmaz O, Doruk C, Ulusan M, Demokan S. Evaluation of genetic and epigenetic changes of Tumor Necrosis Factor-Alpha gene in larynx cancer. Pathol Res Pract. 2022; 238: 154085. [Crosref]
34. Akmansu M, Unsal D, Bora H, Elbeg S. Influence of locoregional radiation treatment on tumor necrosis factor-alpha and interleukin-6 in the serum of patients with head and neck cancer. Cytokine. 2005; 31: 41-5. [Crosref]
35. Tamatani T, Azuma M, Ashida Y, Motegi K, Takashima R, Harada K, et al. Enhanced radiosensitization and chemosensitization in NF-kappaB-suppressed human oral cancer cells via the inhibition of gamma-irradiation- and 5-FU-induced production of IL-6 and IL-8. Int J Cancer. 2004; 108: 912-21. [Crosref]

36. Li Y, Zhang Y, Liu DB, Liu HY, Hou WG, Dong YS. Curcumin attenuates diabetic neuropathic pain by downregulating TNF-α in a rat model. Int J Med Sci. 2013; 10: 377-81. [Crosref]

37. Yang C, Tang H, Wang L, Peng R, Bai F, Shan Y, et al. Dimethyl Sulfoxide Prevents Radiation-Induced Oral Mucositis Through Facilitating DNA Double-Strand Break Repair in Epithelial Stem Cells. Int J Radiat Oncol Biol Phys. 2018; 102: 1577-89. [Crosref]

Comparison of Heavy Metal and Trace Element Levels in Inferior Nasal Concha of People Living in Rural and Urban Regions

Original Investigation

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Abstract

Objective: Heavy metal exposure has recently become a problem due to the increasing environmental pollution as urbanization expands. This prospective cross-sectional study was conducted to compare levels of heavy metals in the nasal concha of the patients living in urban and rural who underwent partial inferior concha resection.

Methods: Sixty-seven patients were divided into two groups: 38 rural patients and 29 urban patients. Partial inferior turbinate resection was performed in these patients with turbinate hypertrophy, and these tissues were examined for heavy metal levels. Lead (Pb), cadmium (Cd), zinc (Zn), copper (Cu), and manganese (Mn) levels were measured in inferior nasal concha by inductively coupled plasma- optical emission spectrometry.

Results: The levels of Cu (0.24±0.048 vs. 0.06±0.019 μg/g) and Zn (3.29±0.69 vs. 0.44±0.14 μg/g) of the rural patients were significantly higher compared to urban patients ($p<0.001$). There was no significant difference in the Cd level between groups. Pb (0.024±0.009 vs. 0.008±0.0002 μg/g) and Mn (0.273±0.01 vs. 0.174±0.05 μg/g) levels of urban patients were significantly higher than rural patients ($p<0.001$). Significance was considered at $p<0.05$.

Conclusion: Heavy metals accumulate in the nasal concha at different rates in rural and urban areas. In pathologies with unclear pathophysiology and potential for heavy metal accumulation, such as air pollution, it may be helpful to indicate the presence of heavy metals in the nasal turbinate's and measure their amounts for diagnostic purposes.

Keywords: Air pollution, heavy metals, nasal mucosa, spectrophotometry, turbinates, inductively coupled plasma-optical emission spectroscopy

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Introduction

Environmental pollution is a severe problem in industrialized and metropolitan cities, threatening public health (1,2). Each year, 4,2 million people die earlier from heart and respiratory diseases triggered by air pollutants (World Health Organization-2008) (3). Pollutants that cause the problem and disturb the natural balance include organic substances, industrial wastes, petroleum derivatives, synthetic agricultural fertilizers, detergents, radiation, pesticides, inorganic salts, synthetic organic chemicals, and waste heat. All of these, directly and indirectly,

cause air pollution. Heavy metals are found in almost all of them, mostly in industrial wastes and pesticides.

Elements are present in the human body in pure form or compounded form. Although some elements are essential for human physiology, some of them are toxic, such as lead (Pb), mercury (Hg), and cadmium (Cd). Generally, intoxication occurs through accumulation as a result of prolonged exposure. Heavy metals cause the dysfunction of enzyme systems by binding oxygen, nitrogen, and sulfhydryl groups to proteins, revealing their toxic effects (4). For instance, metalloproteins in the organism contain large amounts of thiol ligands. These ligands have a high affinity for binding elements such as Cd, copper (Cu), and zinc (Zn). Factors such as heavy metal particle size, duration of heavy metal exposure, and age of individuals determine the degree of heavy metal intoxication (5,6).

The nose is the main entrance gate of polluted air to the body (7). Many heavy metals can enter the body through inhaled air. Detection of heavy metal presence in nasal concha tissues may mean that heavy metals in ambient air cause accumulation in nasal mucosal and submucosal tissues by inhalation. Due to the mucociliary activity of the nasal mucous membranes, inhalation and absorption of pollutants can weaken local immune responses in the airways. This study compared heavy metal levels in nasal concha tissues of patients from urban and rural areas.

Methods

Patients and Study Design

Sixty-seven patients (24 females, 43 males) were administered to the otorhinolaryngology outpatient clinic with nasal obstruction. Most of the selected patients had compensatory nasal concha hypertrophy accompanying nasal septum deviation, and partial resection of the inferior concha was scheduled. The patients were divided into rural (n=29) and urban (n=38) groups according to their living areas of at least 15 years after verbal and written informed consent. The prospective cross-sectional study was initiated after obtaining approval Atatürk University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (decision no: B.30.2.ATA.0.01.00/56, date: 28.11.2014) and was conducted in accordance with the Declaration of Helsinki.

Living in a village was taken as a rural area, and living in the city center was taken as an urban area. As those living in the city center and villages of the districts, we would set our patient population target. Among the patients diagnosed with nasal concha hypertrophy and experiencing nasal congestion due to this condition, those scheduled for partial concha resection surgery and agreed to participate in the study were included after verbal and written consent was obtained. Before the surgery, each patient was evaluated with an anterior nasal endoscopic examination and paranasal sinus computed tomography.

The study was conducted in a tertiary university hospital's otorhinolaryngology-head and neck surgery and biochemistry clinics. Patients with diseases that could affect the presence of heavy metals in the nasal concha were excluded. The exclusion criteria were as follows:

- Smokers/ex-smokers,
- Patients under the age of 18 and over 55,
- Patients with nasal polyps or polyposis,
- Patients with allergic rhinitis,
- Patients with nasal involvement of systemic diseases,
- Patients using medication continuously,
- Patients who had undergone any previous surgical intervention (septoplasty, concha radiofrequency ablation, partial resection) in the nasal cavity,
- Patients working in the industry sector,
- Patients working in the city and commuting to the village or vice versa, were excluded from work.

Surgical Procedure

Partial resection of the inferior concha with septoplasty was performed in 58 patients, and only partial resection of the inferior concha was performed in nine patients. All patients were operated on under general anesthesia by the same surgeon, and a standard procedure was performed. Local anesthetic was not applied to the concha tissue before resection. The inferior nasal conchas were first medialized with the Cottle elevator, and then the lower-medial parts were cut using concha scissors. We washed the resected concha pieces with distilled water, removed the mucus, and attached particles mechanically. The tissues taken were transferred to the sterile tubes without contact anywhere and stored at -80 °C (Figure 1).

Measurements of Metal Concentrations

Nasal concha tissues were let to thaw at room temperature. First, conchal bones, if any, were dissected and removed. From the deboned mucosa and submucosal parenchyma tissue, fragments weighing 0.5 g were transferred into a tube and added with 3 mL of acid mixture (HClO4+HNO3, 5:1). The samples were incubated at 95 oC for one hour (8). Solid conchal tissues were hydrolyzed with acid and became liquid at the end of three hours. Solutions were diluted with distilled water to measure heavy metals (Cu, Zn, Cd, Pb, and Mn) spectrophotometrically using the Inductively coupled plasma-optical emission spectrometry (Perkin-

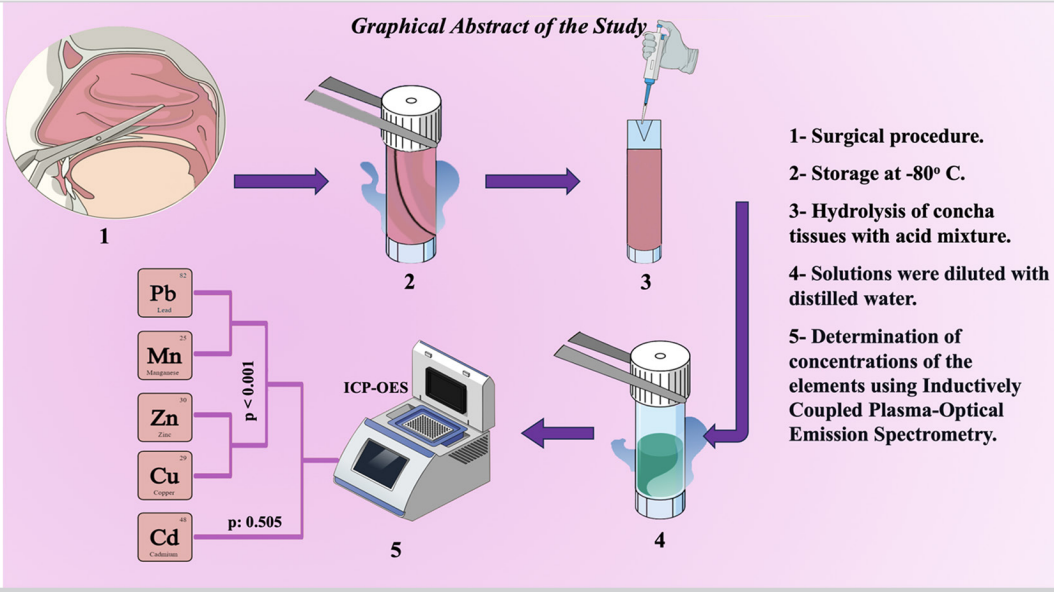

Figure 1. The graphical abstract provides a step-by-step overview of the study, including the surgical procedure, the storage of tissues at -80 degrees, the hydrolysis of tissues with an acid mixture, the schematic representation of the spectrophotometric analysis process with ICP-OES ICP-OES: Inductively coupled plasma-optical emission spectroscopy, Pb: Lead, Cd: Cadmium, Zn: Zinc, Cu: Copper, Mn: Manganese

Elmer, Optima 4300 DV, inductively coupled plasma/optical emission spectroscopy, Waltham, MA). Since the conchal tissues we received were 0.5 g, all results were multiplied by two, and we calculated the heavy metal level in 1 g nasal concha tissue in micrograms (μg).

Statistical Analysis

After confirmation of the normal distribution of the data in the Kolmogorov-Smirnov test, an Independent Samples t-test was used in the comparisons of patient age and Cd, Pb, Cu, Mn, and Zn levels by the patient group (SPSS, version 22, Chicago, IL). Data are presented as a number, percentage, mean, and standard deviation. For the comparisons of individuals according to gender, the Independent Samples t-test was used for continuous variables and the chi-square test for categoric variables. Independent Samples t-test was used to analyze age by gender, Cd, Pb, Cu, Mn, and Zn in both groups. The Pearson correlation test was used to examine the relationship between continuous variables. Significance was considered at $p<0.05$.

Results

There was no difference in the mean age (p=0.991; Table 1) and gender distribution between the groups (p=0.991; Table 1). The age distribution of the rural group was 18-52 (29.3±9.4), and the urban group was 18-55 (29.1±9.8). There were 17 males (58.6%) and 12 females (41.4%) in the urban group, 26 males (68.4%) and 12 females (31.2%) in the rural group.

Cu (0.24±0.048 μg/g) and Zn (3.29±0.69 μg/g) levels of rural patients were significantly higher than Cu (0.06±0.019 μg/g) and Zn (0.44±0.14 μg/g) levels of urban patients (p<0.001, p<0.001, Table 2). The Cd (0.034±0.014 μg/g) level of the rural patients was similar to the Cd level (0.032±0.013 μg/g)

Table 1. Comparison of gender and age distribution between groups

		Female, n=24	Male, n=43	p-value
Age, mean±SD		28.67±9.323	29.37±9.759	0.774*
Urban		12 (31.6%)	26 (68.4%)	0.407**
Rural		12(41.4%)	17(58.6%)	
ELements (μg/g)	Cd, Mean±SD	0.03±0.014	0.032±0.013	0.792*
	Pb, Mean±SD	0.016±0.009	0.014±0.010	0.555*
	Cu, Mean±SD	0.157±0.101	0.164±0.090	0.790*
	Mn, Mean±SD	0.101±0.078	0.114±0.085	0.541*
	Zn, Mean±SD	1.840±1.518	2.172±1.515	0.394*

*Independent Samples t-test, **Chi-square test, SD: Standard deviation, Pb: Lead, Cd: Cadmium, Zn: Zinc, Cu: Copper, Mn: Manganese

of the urban patients (p=0.505, Table 2). Pb (0.024±0.009 µg/g) and Mn (0.273±0.01 µg/g) levels of the urban group were significantly higher than Pb (0.008±0.0002 µg/g) and Mn (0.174±0.05 µg/g) levels of the rural group (p<0.001, p<0.001, Table 2, Figure 2).

Heavy metal levels in rural and urban patients were independent of age and gender. When the two groups were compared, we detected that the difference between the heavy metal levels occurred due to the residence difference (Table 3).

Discussion

Air pollution is considered a general health hazard. Technologies that facilitate our current world release various pollutants into the atmosphere. Technological products increase the concentration of air pollutants in the atmosphere, containing heavy metals harmful to plants, animals, and humans. When specific risk factors such as genetics, diet, and lifestyle come together with environmental factors, the negative impact of air pollution on human health is likely to increase (9). For the individual risk assessment of environmental hazards, showing the physical presence of the substances in the body or the negative functional results is essential. The nasal cavity is a usual gateway to the human body for air pollutants and is a well-known target site for toxicity caused by air pollutants (7). This study reported compassion of levels of heavy metals in nasal conchal tissues in patients living in rural and urban areas.

Few studies examine the relationship between nasal mucous membranes, air pollution, and heavy metals. Şenvar (10) compared serum Cu and Zn levels in the patients with atrophic rhinitis and healthy people and reported higher serum Cu levels and lower serum Zn levels in the patient group. A study compared (11) trace elements on the nasal lower concha and septum. There was an age-related increase in Pb levels in both tissues and decreased Zn levels. In another study (12), exposure to urban pollution in adults in Mexico has increased the proliferation rate in nasal cells, a risk factor for developing neoplasia.

Table 2. Element levels in inferior nasal concha tissues by rural and urban residence

Elements	Rural*	Urban*	t	p-value**
Cd	0.034±0.014	0.032±0.013	0.67	0.505
Pb	0.008±0.0002	0.024±0.009	-8.55	<0.001
Cu	0.24±0.048	0.06±0.019	19.25	<0.001
Mn	0.174±0.05	0.273±0.01	17.45	<0,001
Zn	3.29±0.69	0.44±0.14	24.19	<0.001

*Mean±standard deviation, **Independent Samples t-test, Cd: Cadmium, Cu: Copper, Mn: Manganese, Zn: Zinc, Pb: Lead

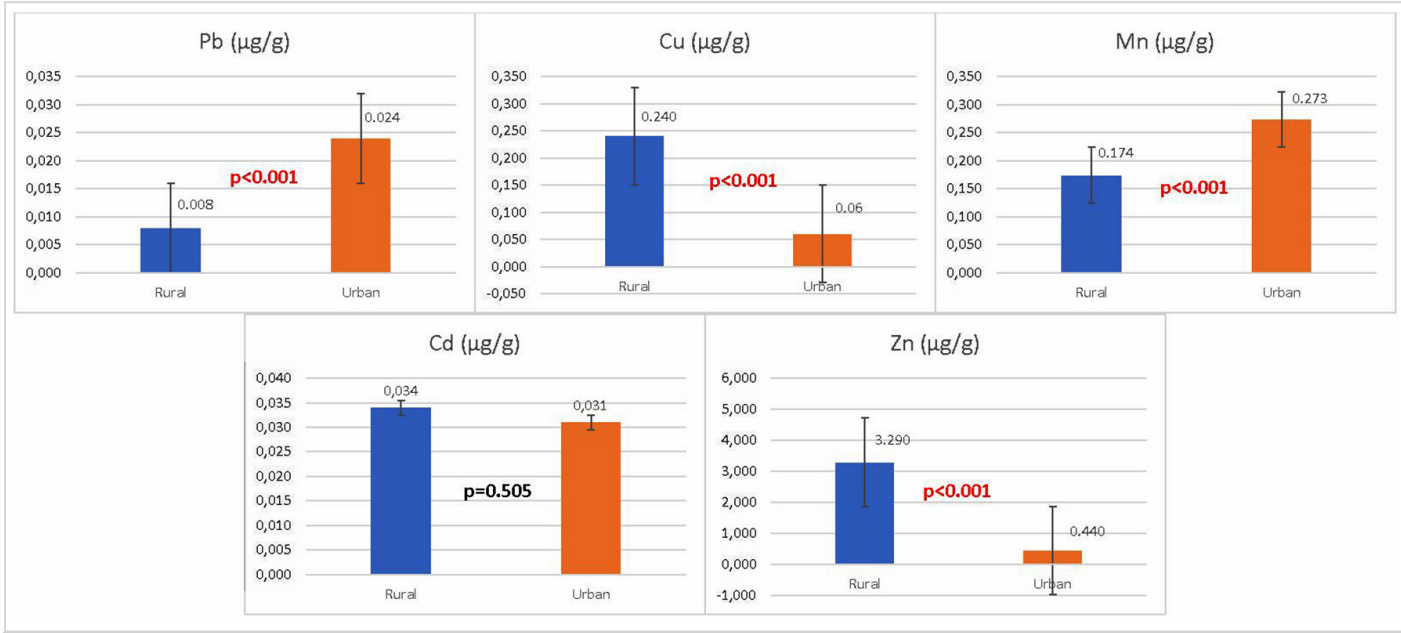

Figure 2. This is a graphic representation of heavy metal levels of Pb, Cu, Mn, Cd and Zn, where there is a statistically significant difference between the levels of the two groups
Pb: Lead, Cu: Copper, Mn: Manganes, Cd: Cadmium, Zn: Zinc

Table 3. Correlation between age and element levels

Age	Cd	Pb	Cu	Mn	Zn
r	-0.14	-0.05	-0.02	0.01	0.01
p-value*	0.26	0.67	0.87	0.99	0.97

*Pearson correlation test, Pb: Lead, Cd: Cadmium Zn: Zinc, Cu: Copper, Mn: Manganese

Calderon-Garciduenas et al. (13), found significant differences in biopsies from nasal mucosa of children exposed to outdoor pollutants compared with a healthy control group. Children exposed to polluted air had more complaints about upper airways, such as epistaxis, nasal congestion, dryness, and crusting. As expected in ENT examinations, abnormal nasal mucosal findings such as increased hyperemia and bleeding points in the nasal mucosa, purulent mucus, and sinusitis were observed. The authors reported basal cell hyperplasia, a decrease in ciliary epithelial cell and goblet cell count, submucosal neutrophil infiltration, squamous metaplasia, and dysplasia histopathological analysis of nasal mucosa biopsies of children exposed to air pollutants.

In rural regions, air pollution is rare and may be caused by pesticides and fertilizers in the agricultural sector (14). Metropolitan locations have more air pollution than rural areas owing to cars, industry, and industrial facilities. Traffic density and diesel and gasoline engine exhaust emissions are the primary sources of air pollution in densely populated metropolitan areas (15,16). CO, SO2, ozone, NO2, and lead are major outdoor air pollutants (14). Ultrafine particles are abundant in city air pollution, and their health effects are unknown (16,17). Glück et al. (18) examined the cytopathology of the nasal mucosa of individuals chronically exposed to diesel engine emissions. They detected goblet cell hyperplasia and an inflammatory response caused by increased leukocytes and defined this condition as chemical-induced rhinitis.

The major heavy metal in polluted air is Pb (19). Air pollution is caused by exhaust gas, and heavy metals enter the body mainly through inhalation (20). Yilmaz and Zengin (21) investigated heavy metal levels in the leaves of trees in the city center and countryside. The amount of Pb in the samples of the city center was significantly higher than in rural areas, and they associated these higher Pb levels with exhaust gas and air pollution. In another study (22), Suchodoller found that the amount of Pb accumulated in the barley and corn planted next to the road was high. They reported that the amount of Pb in the plants decreased as they moved away from the road, and the effect of traffic was not noticed 30-40 m away from the road. Similarly, in our study, Pb levels in the tissues of rural patients were significantly higher than in rural patients ($p<0.001$). Yousaf et al. (23) evaluated tree barks as a bioindicator to monitor air pollution in downtown Toronto and found high Pb and Mn levels in roadside trees with heavy traffic. Our investigation indicated considerably higher Mn and Pb levels in the urban group.

People are not only exposed to polluted air outdoors. The best-known effect is cigarette smoke, which is an air pollutant inside. In an experimental study (24), significant changes were observed in the nasal mucosa of animals exposed to tobacco smoke. In the study conducted by Öner et al. (25) in which the heavy metal levels in the inferior nasal concha of smokers and non-smokers were compared, heavy metal levels were found to be significantly higher in the smoker group. Disruptions in intercellular tight junction complexes, significant structural changes in cell membranes, and increased infiltration of neutrophils on the nasal mucosa surface had been demonstrated in exposed animals. Cigarette smoke or occupationally exposed smoke is inhaled directly into the body along with the heavy metals it contains and causes the levels of heavy metals in the blood to rise (26). In the present study, patients who were smokers and ex-smokers were excluded.

Exposure to passive smoking is almost as harmful to the upper airway as active smoking (27-29). In the study by Elwany et al. (30), biofilm formation with *S. aureus* was seen in the nasal mucosa of 11 out of 20 children who had been exposed to passive smoking, but only one child in the control group had this happen. In the study conducted by Habesoglu et al. (31), mucociliary clearance was observed to be affected in those exposed to passive smoking. We did not exclude exposure to passive cigarette smoke in our study. We can acknowledge this as a limitation of our study.

Heavy metals inhaled with polluted air cause accumulation in the human body. Heavy metals trigger oxidative stress in the organism, increase reactive oxygen species, lipid peroxidation, and inflammatory cytokines, and exhibit harmful effects (4,32,33). Heavy metal accumulation in the nasal concha can lead to oxidative stress and inflammation in mucosal tissues, weakening immune responses and increasing the risk of infection. This accumulation may serve as a biological indicator for assessing the impact of air pollution on respiratory health. Oxidative stress plays a role in the etiopathogenesis of many diseases. It is a challenge to show the harmful effects of exposure to air pollution on human health with evidence. It is necessary to present the pollutant at the same time above the acceptable concentration in ambient air and human tissue, which is a challenging application in the normal population.

Liu et al. (34) showed that silver, a heavy metal, accumulated in the brain tissue of rats given an intranasal spray form. Another study suggested that Cd could pass from the nasal cavity to the brain via the olfactory nerve and show its neurotoxic effects (35). Again, it is predicted that Mn could cause accumulation via nasal uptake (31). As stated in such studies, demonstrating the presence of heavy metals in the nasal cavity could be helpful in shedding light on the etiology of related diseases.

We only measured five heavy metals, which limits our study. Due to technical constraints, this number is small but can be used for future research on heavy metal alterations. Additionally, the absence of simultaneous measurements of heavy metal levels in patient's blood samples and indicators of heavy metal air pollution in their urban and rural areas can be considered.

One limitation of this study is the absence of histopathological analysis of inferior nasal concha tissues. Including histopathological evaluation could provide insights into cellular or tissue-level alterations associated with heavy metal accumulation. This would allow a deeper understanding of the clinical implications and pathological changes from metal exposure. Future studies could enhance these findings by better correlating histopathological results with metal concentration levels to assess the potential impact on nasal and respiratory health. The study's inability to consider passive smoking status despite excluding active smokers and ex-smokers needs improvement.

Conclusion

When we attribute the cause of a condition to air pollution, but the underlying mechanisms are not yet completely understood, showing the presence of heavy metals in the nasal mucosa can be beneficial. In clinical scenarios where there is evidence of heavy metal accumulation and a clear link to diseases, we can mitigate the occurrence of the diseases by implementing preventive measures in urban areas.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Atatürk University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (decision no: B.30.2.ATA.0.01.00/56, date: 28.11.2014) and the Declaration of Helsinki.

Informed Consent: All participants provided written informed consent for the surgical procedures and study participation.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: F.Ö., H.U., Concept: F.Ö., N.K., H.U., Design: F.Ö., N.K., H.U., Data Collection or Processing: F.Ö., N.K., Analysis or Interpretation: F.Ö., N.K., Literature Search: F.Ö., N.K., Writing: F.Ö., H.U.

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

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Main Points

- Air pollution is more prevalent in urban areas than in rural areas.
- Heavy metals in the inhaled polluted air can accumulate in the nasal mucosa and turbinate tissues.
- The determination of heavy metals in the inferior nasal concha can be considered an indicator of air pollution, and spectrophotometric examination of nasal mucosal tissues can aid in the differential diagnosis of associated diseases.

References

1. Kampa M, Castanas E. Human health effects of air pollution. Environ Pollut. 2008; 151: 362-7. [Crossref]
2. Hankey S, Marshall JD. Urban form, air pollution, and health. Curr Environ Health Rep. 2017; 4: 491-503. [Crossref]
3. GBD 2013 Risk Factors Collaborators; Forouzanfar MH, Alexander L, Anderson HR, Bachman VF, Biryukov S, Brauer M, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015; 386: 2287-323. [Crossref]
4. Öner Ü, Özdemir Ş, Öner F, Akdeniz N. Do heavy metals accumulated in saliva involve in the etiopathogenesis of recurrent aphthous stomatitis? Biol Trace Elem Res. 2020; 198: 46-50. [Crossref]
5. Tchounwou PB, Yedjou CG, Patlolla AK, Sutton DJ. Heavy metal toxicity and the environment. Exp Suppl. 2012: 101; 133-64. [Crossref]
6. Bowler RM, Roels HA, Nakagawa S, Drezgic M, Diamond E, Park R, et al. Dose-effect relationships between manganese exposure and neurological, neuropsychological and pulmonary function in confined space bridge welders. Occup Environ Med. 2007; 64: 167-77. [Crossref]
7. Calderón-Garcidueñas L, Rodriguez-Alcaraz A, Garcia R, Barragan G, Villarreal-Calderón A, Madden MC. Cell proliferation in nasal respiratory epithelium of people exposed to urban pollution, Carcinogenesis. 1999; 20: 383-9. [Crossref]
8. Gasparik J, Dobias M, Capcarova M, Smehyl P, Slamecka J, Bujko J, et al. Concentration of cadmium, mercury, zinc, copper and cobalt in the tissues of wild boar (Sus scrofa) hunted in the western

Slovakia. J Environ Sci Health A Tox Hazard Subst Environ Eng. 2012; 47: 1212-6. [Crossref]

9. Glück U, Gebbers JO. The comet assay of nasal epithelia: measurement of DNA damage for the assessment of genotoxic air pollution. Laryngoscope. 2000; 110: 123-5. [Crossref]
10. Şenvar A. Investigation of zinc and copper levels in patients with atrophic rhinitis. J Exp Clin Med. 1982; 2: 107-15. [Crossref]
11. Krmpotíc-Nemaníc J, Valkovíc V, Jaksíc M, Tomíc S, Nemaníc G. Konzentration der Spurenelemente in der unteren Nasenmuschel und im Septum des Menschen [Concentration of trace elements in the inferior turbinates and in the nasal septum of the human]. Laryngol Rhinol Otol (Stuttg). 1987; 66: 622-4. [Crossref]
12. Calderon-Garcidueñas L, Rodriguez-Alcaraz A, Garcia R, Sanchez G, Barragan G, Camacho R, et al. Human nasal mucosal changes after exposure to urban pollution. Environ Health Perspect. 1994; 102: 1074-80. [Crossref]
13. Calderón-Garcidueñas L, Rodriguez-Alcaraz A, Valencia-Salazar G, et al. Nasal biopsies of children exposed to air pollutants. Toxicol Pathol. 2001; 29: 558-64. [Crossref]
14. Holt GR. Effects of air pollution on the upper aerodigestive tract. Otolaryngol Head Neck Surg. 1996; 114: 201-4. [Crossref]
15. Tobías A, Rivas I, Reche C, Alastuey A, Rodriguez S, Fernandez-Camacho R, et al. Short-term effects of ultrafine particles on daily mortality by primary vehicle exhaust versus secondary origin in three Spanish cities. Environ Int. 2018; 111: 144-51. [Crossref]
16. Pey J, Querol X, Alastuey A, Rodríguez S, Putaud JP, Dingenen RV. Source apportionment of urban fine and ultra-fine particle number concentration in a Western Mediterranean city. Atmos Environ. 2009; 43: 4407-15. [Crossref]
17. Kanninen KM, Lampinen R, Rantanen LM, Odendaal L, Jalava P, Chew S, et al. Olfactory cell cultures to investigate health effects of air pollution exposure: Implications for neurodegeneration. Neurochem Int. 2020; 136: 104729. [Crossref]
18. Glück U, Schütz R, Gebbers JO. Cytopathology of the nasal mucosa in chronic exposure to diesel engine emission: a five-year survey of Swiss customs officers. Environ Health Perspect. 2003; 111: 925-9. [Crossref]
19. Cao Y, Skaug MA, Andersen O, Aaseth J. Chelation therapy in intoxications with mercury, lead and copper. J Trace Elem Med Biol. 2015; 31: 188-92. [Crossref]
20. Karataglis S. Estimation of the toxicity of different metals, using as criterion the degree of root elongation in Triticum aestivum seedlings. Phyton. 1987; 26: 209-17. [Crossref]
21. Yilmaz S, Zengin M. Monitoring environmental pollution in Erzurum by chemical analysis of Scots pine (Pinus sylvestris L.) needles. Environ Int. 2004; 29: 1041-7. [Crossref]
22. Suchodoller A. Untersuchungen uber den bleigehatt von pflanzen in der nane von strassen und uber die aufnahme and translokation von blei durch pflazen. Berichteder Schweizerischen Botanischen Gesellschaft. 1967; 77: 266-308. [Crossref]
23. Yousaf M, Mandiwana KL, Baig KS, Lu J. Evaluation of acer rubrum tree bark as a bioindicator of atmospheric heavy metal pollution in Toronto, Canada. Water Air Soil Pollut. 2020; 231: 1-9. [Crossref]
24. Carson JL, Brighton LE, Collier AM, Bromberg PA. Correlative ultrastructural investigations of airway epithelium following experimental exposure to defined air pollutants and lifestyle exposure to tobacco smoke. Inhal Toxicol. 2013; 25: 134-40. [Crossref]
25. Öner F, Mazlumoğlu MR, Kurt O, Kurt N, Ücüncü H. Quantification of heavy metals in the nasal turbines of smokers and nonsmokers. laryngoscope. 2024; 134: 3562-7. [Crossref]
26. Afridi HI, Kazi TG, Kazi AG, Shah F, Wadhwa SK, Kolachi NF, et al. Levels of arsenic, cadmium, lead, manganese and zinc in biological samples of paralysed steel mill workers with related to controls. Biol Trace Elem Res. 2011; 144: 164-82. [Crossref]
27. De S, Fenton JE, Jones AS, Clarke RW. Passive smoking, allergic rhinitis and nasal obstruction in children. J Laryngol Otol. 2005; 119: 955-7. [Crossref]
28. Elwany S, Saeed YH, Talaat I. Effects of passive smoking on adult nasal respiratory mucosa. J Laryngol Otol. 2013; 127: 977-81. [Crossref]
29. Elwany S, Shewel Y, Bazak R, Talaat I, Elwany M. Quitting smoking reverses nasal mucosal changes. Eur Arch Otorhinolaryngol. 2020; 277: 1691-8. [Crossref]
30. Elwany S, Gamea MA, Talaat I. Passive smoking induces nasal biofilms in children. Int J Pediatr Otorhinolaryngol. 2021; 146: 110755. [Crossref]
31. Habesoglu M, Demir K, Yumusakhuylu AC, Yilmaz AS, Oysu C. Does passive smoking have an effect on nasal mucociliary clearance? Otolaryngol Head Neck Surg. 2012; 147: 152-6. [Crossref]
32. Breeher L, Gerr F, Fuortes L. A case report of adult lead toxicity following use of Ayurvedic herbal medication. J Occup Med Toxicol. 2013; 8: 26. [Crossref]
33. Atila NE, Atila A, Kaya Z, et al. The Role of manganese, cadmium, chromium and selenium on subjective tinnitus. Biol Trace Elem Res. 2021; 199: 2844-50. [Crossref]
34. Liu N, Li Y, Liu L, Liu X, Yin Y, Qu G, et al. Administration of silver nasal spray leads to nanoparticle accumulation in rat brain tissues. Environ Sci Technol. 2022; 56: 403-13. [Crossref]
35. Wang B, Du Y. Cadmium and its neurotoxic effects. Oxid Med Cell Longev. 2013; 2013: 898034. [Crossref]
36. Santamaria AB. Manganese exposure, essentiality & toxicity. Indian J Med Res. 2008; 128: 484-500. [Crossref]

Transconjunctival Endoscopic Repair of a Trapdoor Blowout Fracture in a Child

Case Report

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Abstract

Even facial fractures are common in the pediatric population, and the management of blowout fractures contains various surgical methods. Here, we report a child with a blowout fracture handled with transconjunctival endoscopic repair (TCER). A 9-year-old girl was referred with complaints of left eye swelling and erythema after blunt trauma. Physical examination revealed enophthalmos, hypoesthesia in the left cheek, and restriction of left eye movements upwards and downwards. Computed tomography showed a left orbital blowout fracture with herniation of the inferior rectus muscle and soft tissue into the maxillary sinus. TCER was performed. The patient's eye movements were normal one month after surgery. TCER of the orbital floor is a minimally invasive approach with no visible scar, small incision, less trauma to the orbital tissues, and a clear view of the surgical area. It can be used as a safe and successful alternative for orbital floor repair in the pediatric population.

Keywords: Maxillofacial trauma, orbital fractures, maxillofacial surgery, endoscopic repair, pediatric otorhinolaryngology, case report

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Introduction

Facial fractures are common after trauma in the pediatric population, and fractures of the orbital walls are one of the most common facial fractures (1-3). Fracture of the orbital floor with an intact infraorbital rim is referred to as a "blowout fracture". It may occur as an isolated fracture or with naso-ethmoid complex fractures. This fracture causes protrusion of orbital content into the maxillary sinus and causes symptoms such as enophthalmos, ophthalmoplegia, numbness due to infraorbital nerve injury, asymmetry of the face, and diplopia (1-8). The management of orbital floor fractures is, therefore, crucial.

Case Presentation

A 9-year-old girl presented with left eye swelling and erythema after blunt trauma in the pediatric emergency clinic and was referred to the department of otorhinolaryngology with a facial trauma. The patient had a blunt trauma by a swing nearly 12 hours ago. She had a nosebleed that was stopped spontaneously, but the eye swelling continued, and she started to have diplopia and nausea. Physical examination revealed an injured mucosa

at the anterior septum on the left side and left eyelid swelling. After the opening of the eyelid, light reflexes were normal on both sides, and visual acuity was checked as normal with finger counting. Eye movement restriction was seen with upward and more in downward gaze, and enophthalmos was detected. Paresthesia of the infraorbital nerve distribution was detected. Urgent maxillofacial computerized tomography showed a left orbital floor fracture (blowout fracture) with herniation of the inferior rectus muscle and soft tissues into the maxillary sinus (Figure 1).

Surgical intervention with a minimally invasive endoscopic approach was planned. Under general anesthesia, a small transconjunctival incision was done (Figure 2a), with a 0-degree endoscope. The periosteum of the inferior orbital rim was identified and elevated under endoscopic vision. Subperiosteal elevation continued posteriorly, and a trapdoor defect with an entrapped inferior rectus muscle was seen clearly with the endoscope (Figure 2b). Fracture lines involving the infraorbital canal and causing paresthesia at the left maxillary side, entrapped muscle and soft tissues were released under endoscopic vision carefully (Figure 2c). With a brain retractor, all orbital content was gently retracted superiorly, orbital defect edges were exposed with scope, and reconstruction was done. Since the defect was not larger than 30% of the orbital floor, we decided to reconstruct it with a synthetic acellular collagen dura patch. A dura patch nearly two times larger than the defect area was prepared and inserted under endoscopic vision (Figure 2d), and all retractors were released. The transconjunctival incision was sutured. Forty mg prednisolone was administered intravenously to reduce the orbital tissue edema. The patient had antibiotic eye drops three times daily for one week.

Five days after surgery, eye movements were already better, and upward gaze improved, but the patient still had diplopia and pain with eye movements (Figure 3.a,b). One month after surgery, the patient had normal eye movement with functional training, and diplopia was resolved completely. Written informed consent was obtained from the parents of the patient for the publication of this case report and the accompanying images.

Discussion

Due to the elasticity of bone in the pediatric population, a specific type of orbital floor fracture known as a "trapdoor fracture" can occur. This fracture results when the inferiorly displaced broken bone attempts to return to its original position, leading to entrapment of orbital contents within the fracture line (2). If an extraocular muscle becomes entrapped, it may cause restricted eye movements, diplopia, and the oculocardiac reflex (manifested as nausea, vomiting, and bradycardia) (2,6-8).

There are different approaches described in literature, such as transcaruncular, subciliary, and transconjunctival, and trans maxillary approaches. To avoid cutaneous incisions and external scars on the face, the transconjunctival approach is the best method, especially in pediatric cases. Still, a risk of lower eyelid retraction and ectropion may rarely occur (9,10). Surgical indications for orbital floor fractures are

Figure 1. Maxillofacial computed tomography coronal sections show fracture lines with herniated orbital content and entrapped inferior rectus muscle. Close relationship with infraorbital canal (white arrow: fracture line, black arrow entrappedorbital soft tissues and muscle)

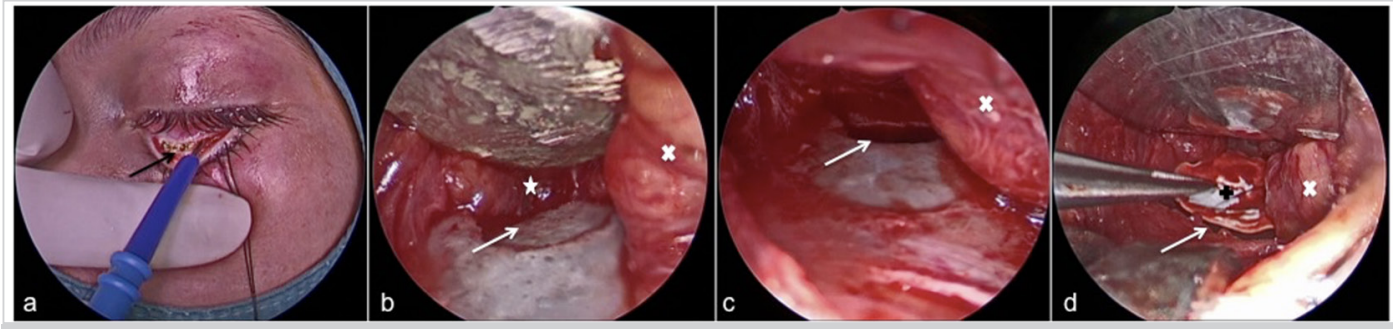

Figure 2. Intraoperative view **a.** transconjunctival incision **b.** endoscopic view of fracture line, trapdoor fracture and entrapped muscle **c.** endoscopic view after release of entrapped tissues and full edges of bony defect **d.** repair with an acellular collagen dura patch (black arrow: incision, white arrow: trap-door fracture, white star: entrapped muscle, x: orbital fat, +:acellular collagen graft)

Figure 3. a. Preoperative eye examination eye movement limitations with infraorbital erythema **b.** Postoperative early outcome (5 days later): better eye movements with no visible scars but still some discomfort in eye movements.

limitations of eye movement, enophthalmos, bony defects in the orbital floor, and herniation of orbital-periorbital content (5,6,8,9). If oculo-cardiac reflex occurs due to a trapdoor fracture, an urgent intervention is required (8,9). Most surgeons favor earlier intervention in the pediatric age group. Late interventions may affect facial development and vision. Multiple studies showed that early intervention (in 48 hours after trauma) may result in improved eye motility in the long-term (5,6,8,9). Surgical intervention aims for reconstruction of the fracture side (revision of fractured bone or using graft for bony defect), release of herniated, entrapped tissue (6-10). Chang et al. (10) reported a series of adult and pediatric patients with combined medial and inferior wall fractures repaired with transcaruncular and transconjunctival approaches. Koryczan et al. (4) reported a series of pediatric patients with blowout fractures and concluded that the severity of posttraumatic enophthalmos does not affect surgical outcomes and that transconjunctival access is the optimal approach in children. Broyles et al. (8) had a large series with 72 pediatric patients and stated that surgical intervention improves enophthalmos but won't affect visual outcomes if there is visual acuity. The study also showed that patients with only mild enophthalmos without any other findings could be managed conservatively. Valente et al. (9) reported a 1-year-old case in which they performed a transconjunctival approach under direct vision and showed early intervention is crucial in the pediatric population due to lack of proper expression of their complaints and to achieve the best outcome.

Endoscopes are primarily used for combined endonasal and open approaches to address inferior orbital wall and medial wall fractures. Although the transconjunctival approach allows direct visualization, our case demonstrates that use of endoscopes offers advantages, including a smaller incision, a clear view of bony defect edges, minimally invasive release of entrapped muscle, and precise graft positioning.

Various materials are suitable for bony reconstruction in the pediatric population, including autologous bone, resorbable materials, and non-resorbable materials (2-4,6,8). Non-resorbable materials may interfere with the normal growth of the facial skeleton and should be used with caution. In our case, an acellular collagen graft provided effective mechanical support for the orbital soft tissues.

Conclusion

Endoscopic transconjunctival repair of the orbital floor is a minimally invasive approach that leaves no visible scar, requires a small incision, causes less trauma to orbital tissues, and offers a clear view of the entire surgical field. It represents a safe and effective alternative for orbital floor repair in the pediatric population.

Main Points

- Orbital fractures are common following maxillofacial trauma in children.
- Pediatric orbital floor fractures require early diagnosis and treatment to achieve the best functional outcome.
- We presented a blowout fracture treated with transconjunctival endoscopic repair in the pediatric population.
- Endoscopic transconjunctival repair of the orbital floor is a minimally invasive treatment with clear visibility of the whole surgical area.
- It may be used as a safe and successful alternative surgical method for orbital floor repair in pediatric population.

References

1. Farwell DG, Strong EB. Endoscopic repair of orbital floor fractures. Facial Plast Surg Clin North Am. 2006;14:11-6. [Crossref]
2. Grant JH 3rd, Patrinely JR, Weiss AH, Kierney PC, Gruss JS. Trapdoor fracture of the orbit in a pediatric population. Plast Reconstr Surg. 2002;109:482-9. [Crossref]
3. Balaraman K, Patnaik JSS, Ramani V, Bhat K, Thomas D,

Bharathi RR, et al. Management of white-eyed blowout fracture in the pediatric population. J Maxillofac Oral Surg. 2021;20:37-41. [Crossref]

4. Koryczan P, Zapała J, Gontarz M, Wyszyńska-Pawelec G. Surgical treatment of enophthalmos in children and adolescents with pure orbital blowout fracture. J Oral Sci. 2021;63:129-32. [Crossref]
5. Chung SY, Langer PD. Pediatric orbital blowout fractures. Curr Opin Ophthalmol. 2017;28:470-76. [Crossref]
6. Su Y, Shen Q, Lin M, Fan X. Diplopia of pediatric orbital blowout fractures: a retrospective study of 83 patients classified by age groups. Medicine (Baltimore). 2015;94:477. [Crossref]
7. Yang HW, Bae JH, Lee HC. The postoperative recovery of ocular motility in pediatric blow-out fracture. J Korean Ophthalmol Soc. 2003; 44:259-64. [Crossref]
8. Broyles JM, Jones D, Bellamy J, Elgendy T, Sebai M, Susarla SM, et al. Pediatric orbital floor fractures: outcome analysis of 72 children with orbital floor fractures. Plast Reconstr Surg. 2015; 136: 822-8. [Crossref]
9. Valente L, Tieghi R, Elia G, Galiè M. Orbital fractures in childhood. Ann Maxillofac Surg. 2019; 9: 403-6. [Crossref]
10. Chang M, Yang SW, Park JH, Lee J, Lee H, Park MS, et al. Using the endoscopic transconjunctival and transcaruncular approach to repair combined orbital floor and medial wall blowout fractures. J Craniofac Surg. 2017;28:963-6. [Crossref]

Commentary on "3D Model for BPPV Diagnosis and Treatment"

Letter to the Editor

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Dear Editor,

We have read with great interest the article published by Güneri et al. (1) in the August 2022 issue of your journal. Benign paroxysmal positional vertigo (BPPV) is one of the most common causes of peripheral vertigo (2). However, understanding the pathophysiology of BPPV and visualizing therapeutic maneuvers remain challenging. Consequently, various illustrations, animations, and mobile applications have been developed to elucidate the pathophysiology of BPPV (3). This study, which represents BPPV using a three-dimensional model, is particularly valuable and unique in demonstrating the anatomy of the semicircular canals and the movement of otoliths during therapeutic maneuvers.

The authors utilized an existing 3D model design to reconstruct the vestibular structure and printed it using a 3D printer. The semicircular canals were placed in appropriate regions of the vestibule using transparent tubing. However, in the provided 3D model, the points where the semicircular canals connect to the vestibule were designed as sealed (https://www.printables.com/model/2800-fluid-filled-vestibular-apparatus-for-vertigo-educ#preview.file.5ZpP4).

Within the tube representing the lateral semicircular canal, sand particles were added to simulate otoliths. Although these particles could move within the canal, they could not exit the non-ampullary end into the utricle. Instead, they accumulated at the terminal part of the canal. In this scenario, for example, during a therapeutic barbecue roll maneuver for a right lateral canal canalithiasis model, when the patient is rotated 90° to the left from the roll position, the sand particles would halt at the non-ampullary end. With two additional 90° leftward rotations, the otoliths would fail to transition to the utricle due to the sealed utricular connection. As a result, they would fall back into the canal under the influence of gravity, preventing an accurate simulation of the maneuver.

The authors noted the absence of a reconstructed cupula and the inability to demonstrate the ocular movements induced by head motion as limitations of

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their study. We believe that modifying the existing 3D design using software (e.g., Fusion 360, Autodesk) to create openings at the junctions where the semicircular canals connect to the utricle would allow otoliths to transition into the utricle, enabling a more accurate simulation of the maneuvers. Furthermore, by adding such openings to the non-ampullary ends of all three semicircular canals, the model could, for the first time, demonstrate canal switch during maneuvers on a 3D platform. This enhancement would contribute significantly to understanding the pathophysiology of BPPV and visualizing therapeutic maneuvers.

References

1. Güneri EA, Hancı S, Olgun Y, Mungan Durankaya S. 3D model to understand the diagnosis and treatment of horizontal canal BPPV. Turk Arch Otorhinolaryngol. 2022; 60: 102-4. [Crossref]
2. Çoban K, Yiğit N, Aydın E. Benign paroxysmal positional vertigo in pregnancy. Turk Arch Otorhinolaryngol. 2017; 55: 83-6. [Crossref]
3. Dlugaiczyk J, Thiemer M, Neubert C, Schorn BA, Schick B. The aVOR app increases medical students' competence in treating benign paroxysmal positional vertigo (BPPV). Otol Neurotol. 2018; 39: 401-6. [Crossref]

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.Ç., Concept: M.Ç., F.Ö., Design: M.Ç., F.Ö., H.E.Ö., Data Collection or Processing: M.Ç., Analysis or Interpretation: M.Ç., H.E.Ö., Literature Search: M.Ç., F.Ö., H.E.Ö., Writing: M.Ç.

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

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Author's Reply

To the Editor,

Thank you for your interest in our article and for your valuable contributions. As we mentioned in the manuscript, this prototype model was planned only for demonstrating and teaching horizontal canal dynamics. Our work on the model is ongoing and we are working on various additions, including the ones you have suggested, so that all physiopathologic processes can be depicted.

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Integration of Large Language Models as an Adjunct Tool in Healthcare

Letter to the Editor

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Dear Editor,

I read with great interest the recent article titled "Evaluating the Performance of ChatGPT, Gemini, and Bing Compared with Resident Surgeons in the Otorhinolaryngology In-service Training Examination" published in your journal (1). The study offers valuable insights into the evolving role of large language model (LLM) in healthcare.

The study's comparative evaluation of Artificial intelligence (AI)-driven language models with resident surgeons is both timely and significant. It highlights the fact that while LLMs, such as ChatGPT and Gemini, exhibit impressive capabilities in answering factual and guideline-based questions. However, they are still far from replacing human expertise (2), especially in highly specialized fields like otorhinolaryngology. The complexity involved in medical decision-making require not only the recall of information but also the ability to apply it in context, an area where general-purpose LLMs like ChatGPT remain limited as it depends on the input (3).

While these tools excel at providing broad and evidence-based responses, they often struggle with the subtleties of case-specific clinical reasoning (4). A summary of potential difference between the LLM and human in various aspect of healthcare is shown in Table 1. Usage of LLMs is an adjunct tool rather than replacements in healthcare education and clinical practice (5). By supporting residents in understanding core concepts, reviewing evidence-based guidelines, or simulating basic diagnostic scenarios, LLMs can serve as a valuable supplementary resource in training environments. However, the integration of AI into medical education and diagnostics must be approached with caution. AI is still some way from being able to reliably make critical healthcare decisions independently. Hence, the use of AI tools should be geared toward enhancing human decision-making rather than substituting it.

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Table 1. Comparative characteristics and capabilities of large language model and human in healthcare

Capability	Large language models	Humans (healthcare professionals)
Knowledge base	Vast, up-to-date knowledge from various medical sources	Extensive, based on education, experience, and continuous learning
Speed of information retrieval	Instant access to large databases of medical knowledge	Slower, relies on memory and manual searching in guidelines or literature
Pattern recognition	Can quickly identify patterns from large datasets	Relies on experience and intuition, better at recognizing subtle, complex cues
Accuracy of diagnosis	Dependent on data quality and training	Typically, higher in complex or ambiguous cases due to clinical judgment
Contextual understanding	May struggle with nuanced patient context (e.g., social, emotional factors)	Rich understanding of patient context, holistic assessment
Handling uncertainty	May provide probabilistic answers, lacks real-world situational judgment	Can navigate uncertainty with experience and clinical reasoning
Ethical decision making	Follows predefined ethical guidelines, no moral reasoning	Uses professional judgment to make complex ethical decisions
Personalization	Limited ability to tailor advice to individual lifestyles or preferences	Highly personalized care based on individual patient histories, preferences, and values
Continuous learning	Can be updated with new data, faster	Constant learning through practice, research, and professional development, slower
Creativity in problem-solving	Limited to predefined algorithms and data	Can innovate, adapt, and think creatively in complex situations
Communication skills	Provides clear, factual, but impersonal communication	Communicates with empathetic way with patients and colleagues
Legal accountability	No legal responsibility, tools to assist but not autonomous	Legally accountable for decisions and patient outcomes
Handling rare/unseen cases	May provide incorrect or incomplete information due to lack of specific data	Can seek further expertise or explore innovative solutions for rare conditions
Adaptation to new research	Dependent on updates and retraining	Continuous adaptation to new research through clinical practice and guidelines

Footnotes

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References

1. Mete U. Evaluating the performance of chatgpt, gemini, and bing compared with resident surgeons in the otorhinolaryngology ın-service training examination. Turk Arch Otorhinolaryngol. 2024; 23: 6248-57. [Crossref]
2. Homolak J. Opportunities and risks of ChatGPT in medicine, science, and academic publishing: a modern Promethean dilemma. Croat Med J. 2023; 28: 64:1-3. [Crossref]
3. Yuan M, Bao P, Yuan J, Shen Y, Chen Z, Xie Y, et al. Large language models illuminate a progressive pathway to artificial intelligent healthcare assistant. Medicine Plus 2024; 1: 100020. [Crossref]
4. Meng X, Yan X, Zhang K, Liu D, Cui X, Yang Y, et al. The application of large language models in medicine: A scoping review. iScience 2024; 23: 109713. [Crossref]
5. Ullah E, Parwani A, Baig MM, Singh R. Challenges and barriers of using large language models (LLM) such as ChatGPT for diagnostic medicine with a focus on digital pathology - a recent scoping review. Diagn Pathol. 2024; 27: 19: 43. [Crossref]

2024 Reviewer Index

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Müge Özçelik Korkmaz
Müzeyyen Yıldırım Baylan
Nadir Yıldırım
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Nesibe Gül Yüksel Aslıer
Nithin Prakasan Nair
Nuray Bayar Muluk
Oğuz Kuşçu
Onur İsmi
Orhan Özturan
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Öner Sakallıoğlu
Özer Erdem Gür
Özge Çaglar Çil
Özgür Sürmelioğlu
Özgür Yörük
Özlem Midik
Özlem Yağız Agayarov
Patrick James Bradley
Raja Rajan Venkatesan
Rasim Yılmazer
Rita Gama
Saime Güzelsoy Sağıroğlu
Seda Türkoğlu Babakurban
Seher Şirin
Selim Sermed Erbek
Semra Aytürk Salt
Serdar Özer
Serpil Mungan Durankaya
Sibel Yıldırım
Sinan Atmaca
Sophia Amalanathan
Sreeram Mp
Sülen Sarıoğlu
Süleyman Özdemir
Şemsettin Okuyucu
Togay Müderris
Uygar Levent Demir
Uzdan Uz
Ülkü Tuncer
Vivek Sasindran
Vural Akın
Yavuz Selim Yıldırım
Yeşim Başal
Yüksel Olgun
Zahide Mine Yazıcı