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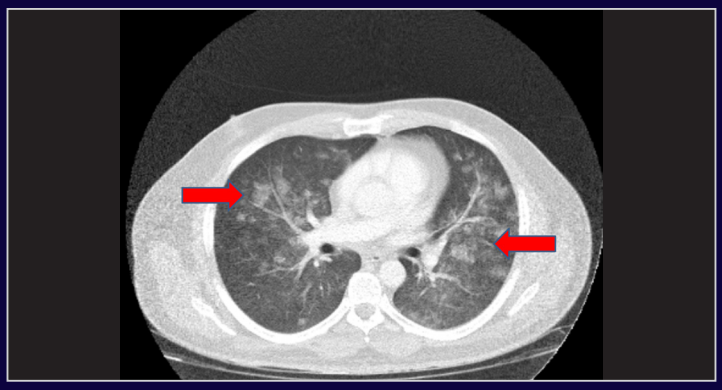

Rare Cause of Severe Dyspnea After Tracheotomy-Negative Pressure Pulmonary Edema

Page: 138-141

Original Investigations

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Turkish Archives of Otorhinolaryngology
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Owner and Responsible Manager on behalf of the Turkish Otorhinolaryngology Head and Neck Surgery Society / Türk Kulak Burun Boğaz ve Baş Boyun Cerrahisi Derneği adına Sahibi ve Sorumlu Yazı İşleri Müdürü: Özgür YİĞİT • Publication Type: Yerel süreli / Local periodical • Basım yeri / Printed at: Matsis Matbaa Hizmetleri San. ve Tic.Ltd.Şti, Tevfikbey Mah., Dr. Ali Demir Cad. No: 5, 34290 Sefaköy, Turkey (+90-212-624 21 11) • Basım tarihi / Printing Date: Eylül 2020 / September 2020 • Türk Kulak Burun Boğaz ve Baş Boyun Cerrahisi Derneği tarafından yayımlanmaktadır. Published by Turkish Otorhinolaryngology Head and Neck Surgery Society, Çobançeşme Sanayi Cad. No: 11 Nish İstanbul A Blok D: 8 Yenibosna, İstanbul, Turkey (+90 212 233 11 26)

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Turkish Archives of Otorhinolaryngology
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International Editorial Board

Turkish Archives of Otorhinolaryngology
Türk Otorinolarengoloji Arşivi

Turkish Archives of Otorhinolaryngology
Türk Otorinolarengoloji Arşivi

Aims and Scope

The Turkish Archives of Otorhinolaryngology (Turk Arch Otorhinolaryngol) is the scientific, peer-reviewed, open-access journal of the Turkish Otorhinolaryngology-Head and Neck Surgery Society since 2001. The journal comprises four issues as March, June, September and December in a volume, and it is published quarterly every year. The journal's publication language is English.

The aim of the journal is to publish qualified original clinical, experimental and basic researches on ear, nose, throat, head and neck diseases and surgery, reviews that contain sufficient amount of source data conveying the experiences of experts in a particular field, case reports, video articles and original images of rare clinical pictures which would shed light on the clinical practice and which were not previously published, letters from the readers and experts concerning the published studies, articles about general practice and subject of the journal with historical content, memories of scientific significance, educative and catechetical manuscripts about medical deontology and publication ethics.

The target audience of the journal includes academic members, specialists, residents and other relevant health care professionals in the field of ear, nose, throat, and head and neck disorders and surgery.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing.

Turkish Archives of Otorhinolaryngology is indexed in **PubMed, PubMed Central, Web of Science (Emerging Sources Citation Index), ULAKBIM TR Index, EBSCO, GALE, CINAHL, J-Gate** and **ProQuest.**

Title: The Turkish Archives of Otorhinolaryngology

Official abbreviation: Turk Arch Otorhinolaryngol

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Open Access Policy

This journal provides immediate open access to its content on the principle that making research freely available to the public supports a greater global exchange of knowledge.

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Abstracting/Indexing Services

Our journal's Abstracting/Indexing services store essential information about articles. In addition, some of our journals' Abstracting/Indexing services archive metadata about the article and electronic versions of the articles.In this way, copies of articles are presented to the scientific

community through these systems as an alternative to journals. This journal's archive has been backed up by PubMed Central (PMC) as from 2015 publications.

Author Self-Archiving Policy

Authors are permitted and encouraged to post their articles on personal and institutional websites after publication (while providing full bibliographic details and a link to the original publication).

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Turkish Archives of Otorhinolaryngology
Türk Otorinolarengoloji Arşivi

Instructions to Authors

CONTEXT

The Turkish Archives of Otorhinolaryngology (Turk Arch Otorhinolaryngol) is a scientific, open access periodical published by independent, unbiased, and double-blinded peer-review principles. The journal is the official publication of the Turkish Otorhinolaryngology Head and Neck Surgery Society, and published quarterly in March, June, September and December. The publication language of the journal is English.

The aim of the journal is to publish qualified original clinical, experimental and basic research on ear, nose, throat, head and neck diseases and surgery, reviews that contain a sufficient amount of source data conveying the experiences of experts in a particular field, case reports and original images of rare clinical pictures which would shed light on the clinical practice and which were not previously published, letters from the readers and experts concerning the published studies, articles about general practice and subject of the journal with historical content, memories of scientific significance, educative and catechetical manuscripts about medical deontology and publication ethics.

EDITORIAL AND PUBLICATION PROCESS

The editorial and publication process of the Turkish Archives of Otorhinolaryngology are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing.

Originality, high scientific quality, and citation potential are the most important criteria for a manuscript to be accepted for publication. Manuscripts submitted for evaluation should not have been previously presented or already published in an electronic or printed medium. The journal should be informed of manuscripts that have been submitted to another journal for evaluation and rejected for publication. The submission of previous reviewer reports will expedite the evaluation process. Manuscripts presented in a meeting should be submitted with detailed information on the organization, including the name, date, and location of the organization.

PEER REVIEW PROCESS

Manuscripts submitted to the Turkish Archives of Otorhinolaryngology will go through a double-blind peer-review process. Each submission will be reviewed by at least two external, independent peer reviewers who are experts in their fields in order to ensure an unbiased evaluation process. The editorial board will invite an external and independent editor to manage the evaluation processes of manuscripts submitted by editors or by the editorial board members of the journal. The Editor in Chief is the final authority in the decision-making process for all submissions. For more detailed information, please read Ethical Policy page of the Journal.

Preprint

The Turkish Archives of Otorhinolaryngology does not consider preprint publications as prior publications. In other words, authors are allowed to present and discuss their findings on a non-commercial preprint server before submission to a journal.

Authors must provide the journal with the preprint server deposition of their article accompanying its DOI during initial submission. If the article is published in the Turkish Archives of Otorhinolaryngology, it is the responsibility of the authors to update the archived preprint and link it to the published version of the article.

AUTHORSHIP

Each person listed as an author should fulfil the authorship criteria recommended by the International Committee of Medical Journal Editors. The ICMJE recommends that authorship is based on the following four criteria:

Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

Drafting the work or revising it critically for important intellectual content; AND

Final approval of the version to be published; AND

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. Also, the authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged in the title page of the manuscript.

Author Affiliations

Authors are expected to state the institutions which they affiliated in the time of the study. Their current affiliation can be added to the article as the corresponding address. Change of affiliation requests will not be implemented after submission. The Turkish Archives of Otorhinolaryngology requires corresponding authors to submit a signed and scanned version of the Authorship Contribution Form during the initial submission process to act appropriately on authorship rights and to prevent ghost or honorary authorship. If the editorial board suspects a case of "gift authorship", the submission will be rejected without further review. As part of the submission of the manuscript, the corresponding author should also send a short statement declaring that he/she accepts to undertake all the responsibility for authorship during the submission and review stages of the manuscript.

Instructions to Authors

Change of Authorship

The Turkish Archives of Otorhinolaryngology reviews the authorship according to the author's declaration in the Title Page; thus, it is the authors' responsibility to send the final order of the complete author names. Requests in the change of authorship (e.g. removal/addition of the authors, change in the order etc.) after submission are subject to editorial approval. Editorial Board will investigate these kind of cases and act following COPE flowcharts.

Change of authorship requests should be submitted to the Editorial Office with an official letter stating the change's reasons. The letter must be signed by all authors and include their approval on the change in authorship. If the request is approved by the Editorial Board, authors need to submit a new Copyright Agreement Form according to the final order list.

DECLARATION OF INTEREST

The Turkish Archives of Otorhinolaryngology requires and encourages the authors and the individuals involved in the evaluation process of submitted manuscripts to disclose any existing or potential conflicts of interests, including financial, consultant, and institutional, that might lead to potential bias or a conflict of interest. Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board. To disclose a potential conflict of interest, the ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all contributing authors. The journal's Editorial Board resolves cases of a potential conflict of interest of the editors, authors, or reviewers within the scope of COPE and ICMJE guidelines.

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The Editorial Board of the journal handles all appeal and complaint cases within the scope of COPE guidelines. In such cases, authors should get in direct contact with the editorial office regarding their appeals and complaints. The Editor in Chief is the final authority in the decision-making process for all appeals and complaints.

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Open access is an approach that supports interdisciplinary development and encourages collaboration between different disciplines. Therefore, the Turkish Archives of Otorhinolaryngology contributes to the scientific publishing literature by providing more access to its articles and a more transparent review process.

MATERIAL DISCLAIMER

Statements or opinions expressed in the manuscripts published in the Turkish Archives of Otorhinolaryngology reflect the views of the author(s) and not the opinions of the editors, the editorial board, or the publisher; the editors, the editorial board, and the publisher disclaim any responsibility or liability for such materials. The final responsibility regarding the published content rests with the authors.

SUBMISSION REQUIREMENTS

• Cover Letter,

• ICMJE Conflict of Interest Statement Form for all contributing authors,

• A separate title page (Title Page should be submitted with all manuscripts and should include the title of the manuscript, name(s), affiliation(s), major degree(s) and ORCID ID of the author(s). The name, address, telephone (including the mobile phone number) and fax numbers and e-mail address of the corresponding author should be clearly listed. Grant information and other sources of support should also be included. Individuals who contributed to the preparation of the manuscript but did not fulfil the authorship criteria should also be acknowledged on the title page),

• Abstract divided into appropriate sections,

• Keywords (For indexing purposes, a list of 4–8 keywords in English is essential),

• Article divided into appropriate sections,

• List of references styled according to "journal requirements",

• A blinded main text (Please exclude all information that may indicate an individual or institution from the main document to ensure a blinded review process),

• The Copyright Agreement and Acknowledgement of Authorship Form (Please submit a wet-signed and scanned copy of the Copyright Transfer Form with your submission),

• Upload your title page and forms in the system to the Potential Conflict of Interest category to ensure a blinded review process,

• Figures (Figures should be submitted as standalone images through the submission system in .JPG or .TIFF format),

• Ethics Committee Approval Statement (with decision/file no, date and name of the institution, for original articles),

MANUSCRIPT PREPARATION

The manuscripts should be prepared in accordance with ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Authors are required to

The presentation of the article types must be designed in accordance with trial reporting guidelines:

Human research: Helsinki Declaration as revised in 2013

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Instructions to Authors

Systematic reviews and meta-analyses: PRISMA guidelines

Case reports: the CARE case report guidelines

Clinical trials: CONSORT

Animal studies: ARRIVE and Guide for the Care and Use of Laboratory Animals

Diagnostic accuracy: STARD Guidelines

Non-randomized public behaviour: TREND

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at www.turkarchotolaryngol.net. Manuscripts submitted via any other medium and submissions by anyone other than one of the authors will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

Authors are required to submit the following:

Copyright Agreement and Acknowledgement of Authorship Form

ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors) during the initial submission. These forms are available for download at turkarchotolaryngol.net.

Policy on Artificial Intelligence Usage:

In our pursuit of scholarly excellence, this policy outlines the principled use of artificial intelligence (AI) in our journal. Authors employing AI tools must transparently disclose their methods, ensuring ethical conduct and full accountability. This policy underscores the importance of transparency, responsible authorship, and the prohibition of AI-generated content as primary sources. Through these guidelines, we maintain the integrity of our academic contributions while embracing the evolving landscape of AI technology.

1. Authorship and AI: Authors utilizing AI tools in manuscript writing, image/graphical element production, or data collection and analysis must transparently disclose the specifics of AI tool usage in the Methods (or equivalent) section of the paper. This disclosure should include details on how the AI tool was employed and which specific tool was utilized. Authors retain full responsibility for the content of their manuscript, even sections generated by an AI tool, and are accountable for any violations of publication ethics. Authors must confirm the absence of plagiarism in text or images produced by AI, ensuring proper attribution and full citations for all quoted material. Nonhuman entities such as artificial intelligence, language models, machine learning systems, or similar technologies are not eligible for authorship.

2. Transparency in AI Usage: Authors are required to openly acknowledge the use of AI tools in their submissions, detailing their role in manuscript creation, image/graphical element production, or data analysis. The involvement of AI, along with the specific tools used, must be clearly stated in the Methods section. Authors are liable for any potential ethical breaches, including plagiarism, in materials generated by AI assistance.

3. Editorial Transparency: Editors incorporating AI tools in the manuscript evaluation process must maintain transparency in their approach. The utilization of AI should be clearly stated by the editorial board to uphold the integrity of the peer-review process.

4. Citation of AI-Generated Material: Citation of AI-generated material as a primary source is not permissible in the Turkish Archives of Otorhinolaryngology. Authors must rely on human-generated content for primary sources, ensuring the credibility and integrity of the research presented.

By adhering to these guidelines, our journal aims to ensure the responsible and transparent integration of artificial intelligence, upholding the highest standards of academic integrity and scholarly rigor in our publications.

Preparation of the Manuscript

Title page: A separate title page should be submitted with all submissions, and this page should include:

The full title of the manuscript, as well as a short title (running head) of no more than 50 characters,

Name(s), affiliations, highest academic degree(s), and ORCID IDs of the author(s),

Grant information and detailed information on the other sources of support,

Name, address, telephone (including the mobile phone number), and e-mail address of the corresponding author,

Acknowledgement of the individuals who contributed to the preparation of the manuscript but who do not fulfil the authorship criteria.

Abstract: An abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, Methods, Results, and Conclusion). Please check Table 1 below for word count specifications.

Keywords: Each submission must be accompanied by a minimum of four to a maximum of eight keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database.

Main Points: All submissions except letters to the editor and clinical images should be accompanied by 3 to 5 "main points" which should emphasize the most noteworthy results of the study and underline the principle message that is addressed to the reader. This section should be structured as itemized to give a general overview of the article. Since "Main Points" target the experts and specialists of the field, each item should be written as plain and straightforward as possible.

Instructions to Authors

Manuscript Types

Original Articles: This is the most essential type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Methods, Results, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Original Articles.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Methods section, and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

Clinical Trials

Turkish Archives of Otorhinolaryngology adopts the ICMJE's clinical trial registration policy, which requires that clinical trials must be registered in a publicly accessible registry that is a primary register of the WHO International Trials Registry Platform (ICTRP) or in ClinicalTrials.gov.

Instructions for the clinical trials are listed below:

A clinical trial registry is only required for the prospective research projects that study the relationship between a health-related intervention and an outcome by assigning people.

To have their manuscript evaluated in the journal, the author should register their research to a public registry at or before the time of first patient enrollment.

Based on most up to date ICMJE recommendations, the Turkish Archives of Otorhinolaryngology accepts public registries that include a minimum acceptable 24-item trial registration dataset.

Authors are required to state a data sharing plan for the clinical trial registration. Please see details under "Data Sharing" section.

For further details, please check ICMJE Clinical Trial Policy.

Data Sharing

As of 1 January 2019, a data-sharing statement is required for the registration of clinical trials. Authors are required to provide a data sharing statement for the articles that reports the results of a clinical trial. The data sharing statement should indicate the items below according to the ICMJE data sharing policy:

Whether individual de-identified participant data will be shared

What data, in particular, will be shared

Whether additional, related documents will be available

When the data will be available, and for how long

By what access criteria will be shared

Authors are recommended to check the ICMJE data sharing examples at http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

While submitting a clinical trial to Turkish Archives of Otorhinolaryngology:

Authors are required to make registration to a publicly accessible registry according to ICMJE recommendations and the instructions above.

The name of the registry and the registration number should be provided in the Title Page during the initial submission.

Data sharing statement should also be stated on the Title Page even the authors do not plan to share it.

The clinical trial and data sharing policy of the journal will be valid for the articles submitted from 1 January 2021.

Editorial Comments: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with a high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, Tables, Figures, Images, and other media are not included.

Review / Systematic Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. While submitting your Review, please confirm that your manuscript is a systematic review and include a statement that researchers have followed the PRISMA guidelines.

Please check Table 1 for the limitations for Review / Systematic Review Articles.

Video Article: Videos should be up to 30 minutes in duration. The video must include audio narration explaining the procedure. All text and audio in the video must be in English. Audio must include narration in clear, grammatically correct English. Videos must be clear, in focus, and without excessive camera movement. Radiographs and other material must not contain any patient-identifiable information. Limited number of slides incorporated into video may be included to provide details of patient history, clinical and laboratory findings.

Video articles should include:

1) Copyright Transfer and Author Declaration Statement Form: This form must indicate that "Patients' Informed Consent Statement" is obtained.

2) Title Page

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Instructions to Authors

3) **Summary:** Summary should point out critical steps in the surgery up to 500 words. This part was published as an abstract to summarize the significance of the video and surgical techniques. The author(s) may add references if it is required.

5) **Video:** Please upload your video to turkarchotolaryngol.net using online submission system. Accepted video formats are Windows Media Video (WMV), AVI, or MPEG (MPG, MPEG, MP4). High-Definition (HD) video is preferred.

6) "Acknowledgements From" should be uploaded separately.

Preparing video content

In order to provide reviewers with a convenient method of accessing video content online, we have restricted video file types to mp, webM and Ogg format. This allows reviewers to view video content easily from all modern browser types without the inconvenience of downloading plug-ins and video players.

Mp4 is the most common online video format, and there are many converters available that will convert other file types to Mp4.

We can recommend using this free online converter to create a suitable mp4 file.

Video file size is limited to 50 Mbytes, and we suggest reducing file size for quicker upload times using this service Compress Mp4.

Please check Table 1 for the limitations for Video Article.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Case Reports.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

Clinical Image: These type of submissions should present a striking image that may challenge and inform readers and contribute to their education. Submissions can include high-quality clinical images, radiology results or surgical images. Please check Table 1 for the limitations for Clinical Images.

Please note that there are author limitations for some article types. Authors should provide a reason for the manuscripts that exceed author limitations. The exception of the articles that are above the author limits is subject to Editorial decision.

Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software, and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labelled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures, too, should be blind. Any information within the images that may indicate an individual

Table 1. Limitations for each manuscript type

Type of manuscript	Author limit	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	N/A	3500	250 (Structured)	30	6	5 or total of 10 images
Review Article	4	5000	250	50	6	10 or total of 15 images
Systematic Review	N/A	5000	250 (Structured)	50	6	10 or total of 15 images
Video Article	N/A	1500	250 (Structured)	10	2	2
Case Report	6	1000	200	10	2	4 or total of 8 images
Letter to the Editor	3	500	No abstract	5	No tables	No media
Clinical Images	3	500	No abstract	5	No tables	3 or total of 7 images

or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in the USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)."

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References

Both in-text citations and references must be prepared according to the Vancouver style.

While citing publications, preference should be given to the latest, most up-to-date publications. Authors are responsible for the accuracy of references. If an ahead-of-print publication is cited, the DOI number should be provided. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed, followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples.

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Journal Article: Erkul E, Cekin İE, Kurt O, Gungor A, Babayigit MA. Evaluation of patients with unilateral endoscopic sinus surgery. Turk Arch Otorhinolaryngol 2012; 50: 41-5.

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Contents

The Effect of Intracochlear and Intratympanic Dexamethasone on Cochlear Implant Impedance

Original Investigation

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Abstract

Objective: This study investigated the impact of different local corticosteroid applications on impedance measurements in patients with cochlear implants.

Methods: The study was designed as a controlled, randomized, and prospective study in which 34 consecutive patients who had undergone cochlear implant surgery were divided into three groups. The first group received intracochlear dexamethasone, in the second group the middle ear cavity was filled with dexamethasone, and the third group did not receive dexamethasone. Intraoperative, postoperative 1st week, 1st month, 3rd month, 6th-month neural response telemetry, and impedances were measured. The measurements were compared by electrode groups representing the different regions of cochlea like basal (1–7), middle (8–13), and apical (14–22) regions.

Results: The intergroup analysis showed no statistically significant differences in impedance measurements of the basal, middle, and apical regions ($p>0.05$). However, the impedances were lower in the two dexamethasone groups, especially in the basal and middle parts. Sixth month impedances were also lower in the dexamethasone groups. There was apparent stability in the impedance of the basal region with the intracochlear application during the first week.

Conclusion: Local dexamethasone applications had a potentially positive impact on the impedance of the basal and middle regions. Patients had lower impedances than the control group during follow-up and at the endpoint. The increase in the apical region may indicate that dexamethasone was not reaching the apical zone in local applications.

Keywords: Cochlear implants, dexamethasone, electrode impedance, fibrosis

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Introduction

One of the common problems with a cochlear implant is the decrease in effectiveness over time due to physiological and mechanical damage in the cochlea (1). The short- and long-term effects of inflammation, osteoneogenesis, and fibrosis limited to the basal turn after surgery have been considered in this condition (2, 3). This is caused by a fibrotic capsule forming around the implant, which in turn results in an immune response to surgical trauma or a foreign body reaction to the platinum-iridium and silicon used in cochlear implants (4, 5). Studies have also shown a correlation between fibrotic tissue and electrode impedance (6). Choi et al. (7) suggested that impedance measurement could be used as a biomarker for cochlear damage.

Animal studies showed that glucocorticoids reduced foreign body reactions and fibrosis, thus increasing the lifespan of the spiral ganglia and the hair cells (8). Corticosteroids have been used for many years in cochlear implant surgeries. Although different systemic and local administration routes have been reported, it is still under development today (9-11).

We aimed to observe the effect of local corticosteroid applications during cochlear implant surgery on impedance.

Methods

A controlled, randomized, prospective clinical trial was planned in patients with cochlear implant surgery (registered with clinicaltrials.com, no: NCT04397354). Pamukkale University Non-invasive Clinical Research Ethics Committee approval was obtained (no: 60116787-020/20945, date: 23.03.2018). All patients signed the written informed consent form. Those with cochlear anomalies were excluded.

Cochlear implant operation was performed under general anesthesia, and 1 mg/kg methylprednisolone was administered intravenously to all patients in addition to anesthetic drugs as a part of routine general anesthesia. The round window soft technique was used to implement the devices. The cases with cochleostomy were excluded. The same cochlear implant electrode model was used in all patients (Cochlear, Inc. CI 422). The cochlear implants were activated after one month.

The patients were randomly divided into three groups for implantation using the random number table method according to the administration of dexamethasone (dex) (4 mg/mL).

1. In the first group, dex was administered slowly with a 27-gauge needle into the cochlea after a round window membrane incision (Group 1, the Cocdex group).

2. In the second group, dex was administered into the middle ear after a round window membrane incision (Group 2, the Middex group).

3. Dex was not administered to the third group (Group 3, control, the Nodex group).

The drug was left in place for three minutes before inserting the electrodes.

Intraoperative neural response telemetry thresholds and impedances were measured. Impedance measurements were repeated at the end of the first postoperative week, and at the first third, and sixth months. Monopolar1+2 (MP1+2) impedance (kOhm), measurements were used for comparison.

The mean of the basal (1–7), middle (8–13), and apical (14–22) electrodes were used for comparison. We also compared the average of all electrodes. The Custom Sound EP 5.0 (5.0.4.136) program provided by Cochlear, Inc. was used for measurement.

Statistical Analysis

All statistical analyses were performed with the SPSS 25.0 software [IBM SPSS Statistics 25 software (IBM Corp.: Armonk, NY, USA)]. Continuous variables were expressed as mean ± standard deviation, median (minimum-maximum values), and categorical variables as number and percent. The Shapiro–Wilk test was used to test for normality. If parametric test conditions were satisfied, the One-Way Analysis of Variance (post-hoc: Tukey test) was used to compare groups. If parametric test conditions were not satisfied, Kruskal–Wallis variation analysis (post-hoc: The Mann–Whitney U test with Bonferroni correction) was used to compare the groups. For pairwise comparisons, if parametric test conditions were satisfied the Repeated Measures ANOVA (post-hoc: Bonferroni test), and if parametric test conditions were not satisfied, the Friedman (post-hoc: Wilcoxon signed-rank test with Bonferroni correction) tests were used. The chi-square test was used to compare categorical variables and $p<0.05$ was considered statistically significant.

Results

Initially, a total of 34 patients were included in the study. Of these, 12 were in Group 1, 12 were in Group 2, and 10 were in Group 3. One patient in Group 1 and one patient in Group 3 were excluded from the study due to noncompliance with follow-up and repetitive measurement times. Three patients in Group 3 in whom the cochleostomy technique was used were also excluded. Due to the pandemic, the 1st-week measurement of one patient, the 1st-month measurement of one patient, the 3rd-month measurement of two patients in Group 1; the 1st-month measurement of one patient, the 3rd-month measurement of one patient in Group 2; and the 1st-week measurements of two patients, the 1st-month measurement of one patient in Group 3 could not be performed on the planned date, the values of these measurements were not used in the analysis (Figure 1).

There were no differences between the groups regarding gender (17 women and 12 men, $p=0.543$) and age ($p=0.688$).

The variations of the mean MP1+2 impedance measurements over time are given in Figure 2.

In the apical zone, impedances reached the highest level, usually at the end of the first month, except in the Cocdex group, and then decreased rapidly in all groups.

In the basal and middle zones, all three groups reached the maximum impedance value at the end of the first month. In the first week, the impedances measured from the basal region were lowest in the intracochlear group (Figure 2). In the first month, impedances were higher in the Nodex group compared to the two dex groups in the basal and middle regions (Figure 2). The statistical comparisons of the time points within the groups are also plotted in Figure 2. Impedances increased until the first month (between t0 and t2) in all regions except for the basal and middle electrodes of the Cocdex roup ($p>0.05$), and these increases were statistically significant ($p<0.05$).

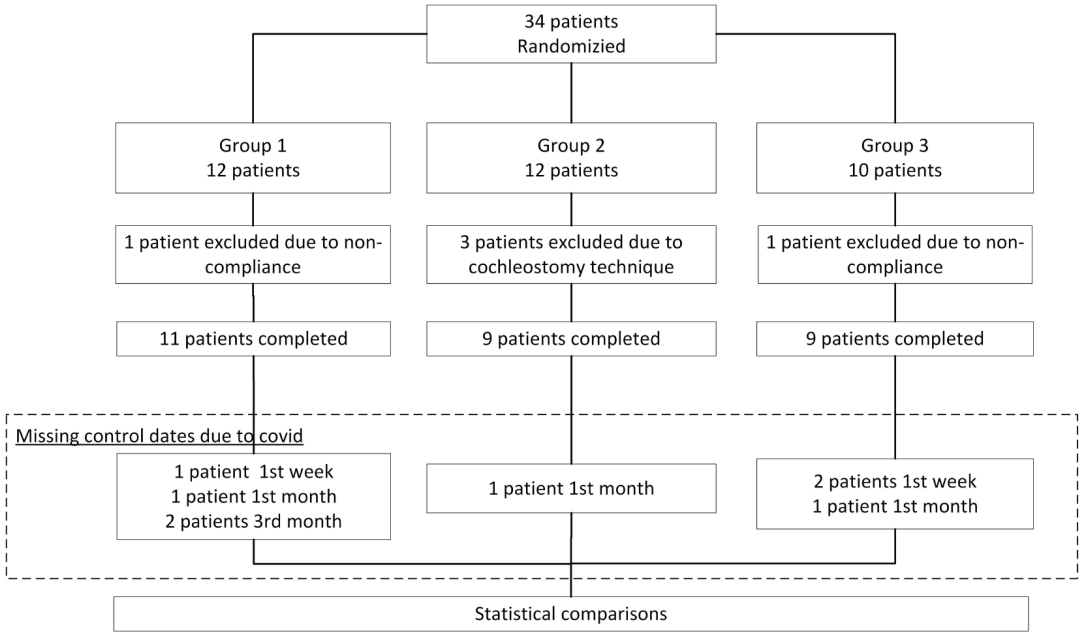

Figure 1. Study design, patient groups, and missing control points

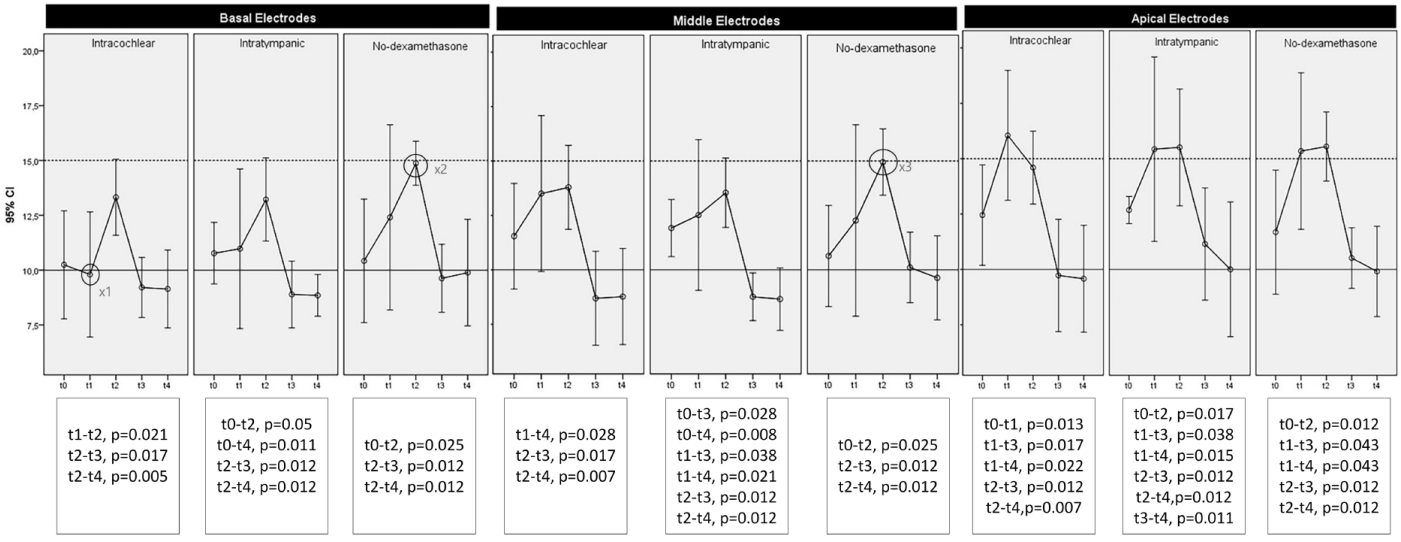

Figure 2. MP 1+2 impedances were compared within groups according to the regions of the cochlea. In the first week, the impedances measured from the basal region were lowest in the intracochlear group (x1). In the first month, impedances were the highest in the Nodex group compared to the two dexamethasone groups in basal and middle regions (x2, x3). The impedance increased until the first month (between t0 and t2) in all regions, and the increases were statistically significant ($p<0.05$), except for the basal and middle electrodes of the Cocdex group ($p>0.05$). In the sixth-month control, impedances were lower in the dexamethasone groups than in the control group. Statistically significant comparisons between time points within the groups are plotted below the graphics (Wilcoxon signed-rank test) (t0: during surgery, t1: first week, t2: first month, t3: third month, t4: sixth month)

No statistically significant results were found between the groups at any time point or in any region ($p>0.05$) (Table 1). The change in the apical region in the 1st week was not significantly faster than in the middle and basal parts. The impedances were lower in the first week in the middle and basal regions. Their highest values were measured at the end of the first month in all three groups. Impedances were higher in the Control (Nodex) group but were not statistically significant ($p>0.05$).

There were also no statistically significant differences when the mean impedances of all electrodes were compared ($p>0.05$).

Table 1. Age and MP1+2 data plotted according to groups

	Group 1 (n=11)						Group 2 (n=9)						Group 3 (n=9)						Kruskal–Wallis sig
	Mean	SD	min	max	med	STE	Mean	SD	min	max	med	STE	Mean	SD	min	max	med	STE	
Age(month)	182.18	192.24	14	604	115	57.96	248.44	244.98	13	741	279	81.66	267.66	238.07	24	660	237	79.37	p=0.688
MP1+2 apikal t0	12.09	2.14	7.86	15.42	12.52	0.65	12.49	0.89	10.98	14.03	12.52	0.30	12.05	2.24	6.34	13.68	12.81	0.75	p=0.959
MP1+2 apikal t1	15.20	3.50	8.85	20.57	15.78	1.11	15.54	4.67	7.25	24.73	16.47	1.56	15.05	3.18	9.63	19.13	15.36	1.20	p=0.972
MP1+2 apikal t2	14.15	2.40	9.05	16.60	14.52	0.76	15.51	3.15	11.31	22.42	15.28	1.11	15.63	1.48	13.39	17.30	15.83	0.52	p=0.362
MP1+2 apikal t3	10.71	3.10	6.74	15.02	11.03	1.03	11.32	2.88	7.93	17.90	10.80	0.96	10.41	1.37	8.23	11.82	10.67	0.46	p=0.904
MP1+2 apikal t4	10.42	2.50	5.65	13.45	10.21	0.75	9.74	3.49	7.24	18.34	8.13	1.16	9.72	1.69	8.07	13.06	9.11	0.56	p=0.420
Friedman test sig	p=0.001						p=0.006						p=0.006						
MP1+2 middle t0	11.14	2.26	6.75	14.03	11.91	0.68	11.69	1.62	9.75	14.00	11.71	0.54	11.00	1.88	6.78	12.63	11.62	0.63	p=0.796
MP1+2 middle t1	12.52	4.33	5.23	18.86	12.54	1.37	12.75	3.93	5.71	15.97	14.56	1.31	11.99	3.90	6.64	17.06	12.38	1.47	p=0.925
MP1+2 middle t2	13.37	2.77	7.45	15.86	14.24	0.87	13.54	1.91	9.83	15.51	14.12	0.67	14.81	1.52	12.78	16.36	15.39	0.54	p=0.315
MP1+2 middle t3	9.92	3.17	5.53	14.28	8.81	1.06	9.13	1.65	6.79	12.10	9.18	0.55	9.99	2.36	5.99	13.99	10.00	0.79	p=0.776
MP1+2 middle t4	9.63	2.51	5.23	12.49	10.86	0.76	8.44	1.73	6.59	11.12	8.83	0.58	9.50	2.52	6.17	13.89	9.65	0.84	p=0.517
Friedman test sig	p=0.001						p=0.002						p=0.038						
MP1+2 basal t0	10.25	2.41	5.48	13.48	10.94	0.73	10.51	1.75	8.44	13.04	9.69	0.58	10.92	2.35	5.49	13.31	11.16	0.78	p=0.712
MP1+2 basal t1	9.82	3.57	5.57	15.96	8.88	1.13	10.52	4.29	4.89	14.76	10.79	1.43	11.84	3.97	7.48	17.62	10.41	1.50	p=0.591
MP1+2 basal t2	12.90	2.80	6.44	15.43	13.89	0.89	13.22	2.27	8.68	16.06	13.81	0.80	14.44	1.55	11.17	15.77	15.07	0.55	p=0.247
MP1+2 basal t3	10.25	2.45	7.89	14.36	9.06	0.82	9.51	2.52	5.88	14.46	9.65	0.84	9.67	2.59	6.93	15.09	9.76	0.86	p=0.708
MP1+2 basal t4	9.54	2.38	6.17	14.02	9.40	0.72	8.84	1.07	6.57	10.26	8.77	0.36	9.61	2.66	6.27	13.36	10.07	0.89	p=0.720
Friedman test sig	p=0.009						p=0.006						p=0.032						
MP1+2 total t0	11.16	2.15	6.70	13.54	12.19	0.65	11.56	1.38	9.76	13.69	11.39	0.46	11.32	2.10	6.20	13.21	11.75	0.70	p=0.991
MP1+2 total t1	12.52	3.36	6.66	17.82	12.11	1.06	12.94	3.88	6.00	18.49	14.01	1.29	12.96	3.47	8.94	17.94	13.50	1.31	p=0.949
MP1+2 total t2	13.47	2.60	7.65	15.86	14.05	0.82	14.09	2.05	9.94	16.79	14.12	0.73	14.96	1.41	12.80	16.22	15.57	0.50	p=0.471
MP1+2 total t3	10.29	2.82	6.82	14.26	9.29	0.94	9.99	1.87	6.86	13.09	10.08	0.62	10.02	1.96	7.05	13.59	9.59	0.65	p=0.979
MP1+2 total t4	9.86	2.28	5.96	12.34	10.35	0.69	9.01	1.74	7.03	12.52	8.77	0.58	9.61	2.08	6.86	12.65	9.52	0.69	p=0.627
Friedman test sig	p=0.002						p=0.002						p=0.026						

t0: During surgery, t1: First week, t2: First month, t3: Third month, t4: Sixth month, SD: Standard deviation, STE: Standard error, sig: Significance, min: Minimum, max: Maximum, med: Median

Discussion

In this prospective, randomized, controlled study, we aimed to measure the effect of different dex applications on tissue inflammation during cochlear implantation by electrode impedance. We found that the intraoperatively measured impedances decreased in the long-term and reached the lowest point, mainly in the 6th month, which was the study time limit. Impedances were lower in the dex groups than in the control group in the basal and middle regions. The stability of impedance at basal electrodes in the first week of the Cocdex group was marked. The first-week impedances of the Middex group were also lower than those of the Nodex group. These findings may be attributed to the local and short-duration effects of corticosteroids. The sharp increase in impedance in the apical electrodes during the first week, even in the dex groups, may indicate that dex was not reaching the apical zones. In all groups, a marked decrease in impedances was observed after the first month, the cochlear implant's activation date. Again, the impedances of the dex groups decreased more than the those of the control (Nodex) group at the endpoint of the study.

A similar hypothesis was tested in guinea pigs. In this study the authors compared the effects of the intratympanic, intracochlear, and systemic administration routes by cytokines and residual hearing. They reported that the intracochlear route had reached the highest drug concentration. Intracochlear dex provided better protection for residual hearing and a less inflammatory response in the cochlea (10). We observed some promising results, especially in the basal region.

The results of animal and human studies with local steroid applications elicited the research on dex eluting electrodes. Astolfi et al. (12) tried a 10% dex eluting electrode on guinea pigs and reported that less tissue growth had been observed. Briggs et al. (3) implanted a dex eluting electrode and followed the patients for two years with MP1+2 impedance measurements. They found that the experimental electrode had lower impedance at all time points and all cochlea regions than the standard electrode. They observed a direct reduction of impedances even in the first week. Our study also found stability in the impedances in the basal region. After the effect of dex had diminished over time, the impedances rose again.

Additional systemic steroids used with dex eluding electrodes were tested (13). Systemic steroids did not show an additional effect over inserting electrodes alone. The authors concluded that the protective effect of steroids was prominent, especially in traumatic insertions. We could not obtain statistically significant results for the use of dex. Perhaps this was due to the atraumatic insertion technique in all patients. Ahmadi et al. (14) also support this conclusion. They said there must be trauma in the cochlea to see the effectiveness of dex. Non-traumatic insertion preserved the cochlea in most animals.

Lee et al. (2) compared different local and systemic applications in an animal implant model. They reported no significant differences between the delivery routes, but that could be effective if used for a longer duration and higher dose. The protective effect of dex had a linear relationship with the concentration of the drug and the time of contact with the round window. Chang et al. (9) reported that 2% dex for 60 minutes had the same protective effect with 20% dex for 30 minutes on guinea pigs.

We observed an increase in impedance in the apical region in the early period in both dex groups. Wei et al. (15) also observed the same increase in the 1st week with an early switch-on technique. In the 8th week, they showed that there was an increasing trend of impedance in all parts of the cochlea and was highest in the basal region. They argued that this was because fibrosis had started on days 2 to 5 after the operation, fibrotic tissue began to dissolve in the second week, and more severe fibrotic tissue formed in the basal region due to trauma. In our study, impedance remained low in the dex groups in the basal region. It might be due to the anti-inflammatory effect of the corticosteroids.

One of the limitations of this study was the coronavirus disease-2019 pandemic. Some patients missed the exact test dates, so we omitted some data from the calculations. Another limitation is the short time between dex administration and implant placement.

Nevertheless, this kind of study in patients is rare. Its advantages are that standard commercial electrodes were used, all operations were done by a single surgeon and the tests by a single audiologist, and only objective parameters were measured.

Conclusion

Although there were no significant differences among the groups, intracochlear and intratympanic applications of dex positively impacted the impedance in the basal and middle regions during the first week. Patients in the dex groups had lower impedances than the control group during follow-up and at the endpoint. The sharp increase in the apical region may indicate that dex was not reaching the apical zone in local applications.

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Main Points

- Local dexamethasone applications had a possible positive impact on the impedance of the basal and middle regions.
- Patients in the dexamethasone groups had lower impedances than the control group during follow-up and at the endpoint.
- The impedance increase in the apical region may indicate that dexamethasone was not reaching the apical zone in local applications.

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Adaptation and Validation of the Turkish Version of the International Tinnitus Inventory

Original Investigation

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Abstract

Objective: Tinnitus is a common auditory symptom that negatively affects the quality of life of individuals. This study aimed to determine the validity and reliability of a Turkish version of the International Tinnitus Inventory (Tr-ITI) for both clinical and research purposes. ITI is a short, easily applicable self-report inventory to measure perceived tinnitus.

Methods: The Turkish translation of the ITI and the Tinnitus Handicap Inventory (THI) were administered to 125 participants aged 19 to 76 with tinnitus complaints for over three months. A routine audiological evaluation was performed, and the psychoacoustic properties of tinnitus were determined. Confirmatory factor analysis (CFA) was performed to construct validity, Cronbach's alpha coefficient was used for the reliability of internal consistency, and retests were administered to participants 15 days after the first measurement.

Results: CFA and inter-item correlations confirmed the unifactorial model. Tr-ITI showed high internal consistency reliability (Cronbach's alpha =0.909). All fit index values showed a good fit. Correlations between the total scores of Tr-ITI and THI were moderate (r=-0.620) and between retest scores were very high (r=0.993).

Conclusion: The Tr-ITI is a valid, reliable, and practical tool for determining tinnitus severity and tinnitus complaints.

Keywords: Otology, tinnitus, surveys and questionnaires, quality of life, validity and reliability, audiology

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Introduction

Tinnitus is the perception of sound, such as ringing, humming, etc., in the ears or in the head without an external acoustic stimulus. It is a very common auditory complaint. Although its incidence varies in various studies, it is seen between 4–37% in adults, and this rate rises to 17–30% in adults aged 50 and over (1, 2). It is known that prolonged duration and increased severity of tinnitus cause different psychological problems ranging from depression and anxiety to suicidal thoughts, as well as attention and concentration difficulties, reduce enjoyment of life, cause sleep problems, affect social activities and relationships, and increase hearing problems (3-8). All of these factors lead to a significant decrease in the quality of life.

Detailed assessment is critical for tinnitus treatment and/or therapy. However, it is very difficult to measure tinnitus objectively as it is a perception that

varies from person to person. The measurement of the psychoacoustic aspects of tinnitus (pitch and loudness matching, minimal masking level, residual inhibition) is an objective measurement. However, the correlation between the psychoacoustic properties of perceived sound as tinnitus and its impact on an individual's life is weak (9). Although the intensity and frequency of the sound perceived by people with tinnitus are similar, tinnitus severity can be found at different levels. Therefore, self-report scales have an important role in the assessment of tinnitus severity. Self-reported tinnitus handicap scales are used in clinical processes such as tinnitus counseling, therapy, and measurement of therapy outcomes (10).

The use of scales/inventories/questionnaires in tinnitus is important in terms of obtaining measurable information, planning therapy, determining the results, providing wide-ranging information, containing standardized questions, and protecting the clinician from medicolegal problems related to subjective complaints such as tinnitus. Thus, most audiology clinics use tinnitus questionnaires to evaluate tinnitus-related handicaps, particularly at the first appointment. Validated questionnaires are evidence-based and cost-effective tools for tinnitus evaluation. There are different questionnaires commonly used worldwide. The Tinnitus Handicap Inventory (THI), the Tinnitus Questionnaire, the Tinnitus Reaction Questionnaire, the Tinnitus Functional Index, and the Tinnitus Handicap Questionnaire are the main scales in tinnitus evaluation (11-15). The THI and the Mini Tinnitus Questionnaire have already been validated in Turkish (16, 17). The International Tinnitus Inventory (ITI) was developed by Kennedy et al. (18) in 2005, inspired by the International Outcomes Inventory-Hearing Aids (IOI-HA). Item format and responses are similar to IOI-HA.

The ITI is a patient-friendly questionnaire with a simple response format (18). The ITI is a time-saving short inventory consisting of only eight items and easy to administer as part of the clinical routine. Its small number of items provides clear and fast information about tinnitus and the difficulties it causes, enabling the clinician to easily determine the most distressing effects of tinnitus (19). The items inquire about the effect tinnitus has on hearing, sleep, enjoyment of life, daily activities, other health problems, peace of mind, other people, and the annoyance tinnitus causes. In this study, we adapted the ITI to Turkish and tested its validity and reliability in the Turkish population without any otologic and neuro-otologic problems.

Methods

The study design and the consent form were approved by the Non-interventional Clinical Researches Ethics Board of Hacettepe University under project no GO 18/1106 (decision no: GO 18/1106-31, date: 27.11.2018). The informed consent form was signed by all participants. The study was conducted according to the principles of the Declaration of Helsinki.

Translation and Cultural Adaptation of the International Tinnitus Inventory

For the cross-cultural adaptation, we followed the guidelines proposed by Guillemin et al. (20) and Beaton et al. (21). In this first step of the study, permissions were obtained from the original ITI developer for translation into Turkish and the validity and reliability process. Commonly used validity and reliability processes were carried out: forward-translation and back-translation, followed by validation testing and reliability testing. The forward-translation of the ITI was done independently by a team of two audiologists and one English linguist-a native Turkish speaker fluent in English. All team members noted the cultural and linguistic details. This team elaborated the semantic, linguistic, cultural, and conceptual properties of all three translations duo with the original version and made a synthesis of the Turkish translations. Then, the translated content was back-translated into English by a native-speaker English linguist. The back-translated version was compared with the original ITI by the designated team of two audiologists and one English linguist, taking into consideration the semantic, conceptual, and cultural aspects. There were no significant differences between the original ITI and the back-translated version and required no revisions. Then, a pilot study was conducted using the final Turkish version with 20 randomly selected participants. Their opinions about the clarity, content, and intelligibility of the questions on the scale were obtained. In line with their recommendation, the Turkish version of the ITI (Tr-ITI) was finalized with minor changes such as revision of suffixes.

Participants and Audiologic Evaluation

One hundred twenty-five adults aged 19 to 76 years with tinnitus complaints for at least three months were included in the study. All participants were literate in Turkish and at the cognitive level to understand and conduct the instructions given for the study. The sample size was determined by the minimum (min) subject-item ratio of 10 (22). Individuals who were referred to the audiology department for hearing and tinnitus evaluation accepted to participate in the study. The routine audiological evaluation was performed for each participant, using a calibrated clinical audiometer (Interacoustics AC 40, Denmark) with Telephonic TDH 49 headphones in a quiet soundproof room. Pure tone audiometry was performed for air conduction thresholds at frequencies between 125–8000 Hz, and bone conduction thresholds at frequencies between 500–4000 Hz. Pure tone average (PTA) was calculated at frequencies between 500–4000 Hz. Psychoacoustic properties of tinnitus (frequency,

loudness, minimal masking level, and residual inhibition) were tested on all participants.

Validity and Reliability

The ITI is an eight-item questionnaire based on the most common complaints of tinnitus patients. It is brief, has a clear and simple response format, and is comparable across languages. Each item is scored on a scale of one to five, with one indicating great difficulty and five indicating no difficulty with tinnitus; i.e., a decrease in the score reflects a more troublesome perception of tinnitus.

In this study, THI was used as a parallel inventory. THI is a commonly used self-report inventory comprising 25 questions about tinnitus complaints to determine the perceived tinnitus handicap severity. THI evaluates tinnitus in functional, emotional, and catastrophic aspects. Each item has "yes", "no" and "sometimes" response choices. The total score ranges between 0-100, and the maximum (max) score means max tinnitus severity.

After the translation step, the validity of the inventory was tested. In this step, Tr-ITI was administered to 125 volunteer participants. They were informed about the inventory and rated the Tr-ITI and THI in a silent room at the clinic.

For the construct validity analysis, confirmatory factor analysis (CFA) was performed to analyze the validity and exploratory factor analysis (EFA) was done to investigate the factor structure of the Tr-ITI. The reliability of internal consistency was interpreted according to Cronbach's alpha coefficient. For evaluating measurement reliability, the correlation between items and the corrected item-total score correlation, the effect on the scale score means, and the change in Cronbach's alpha value when the item is removed were investigated. The test-retest method was used to examine the reliability of the measurement results. The consistency of the inventory was examined based on time, and the correlation between measurements was calculated with a retest. The retests of Tr-ITI were administered to participants 15 days after the first measurement.

Statistical Analysis

Statistical analyses were done using IBM SPSS Version 22 (IBM SPSS Corp.; Armonk, NY, USA), and CFA was done with AMOS (IBM, New York, NY). The normal distribution of scale total scores was examined using the Kolmogorov–Smirnov test. Within the scope of the validity-reliability study of the scale, the Kaiser–Meyer Olkin (KMO) test, EFA, CFA, Cronbach's alpha test, Spearman's correlation test, and item-total correlations were examined. The goodness-of-fit indices were calculated to test the factor structure. A 5% type-I error level was used to understand the statistical significance.

Results

Participants and Audiologic Evaluation

A total of 125 individuals, 66 males aged between 19–71 years (mean ± SD =48.2±13.0) and fifty-nine females aged between 22–76 years (mean ± SD =51.1±12.8) participated in the study. Seventy-two participants had normal hearing, 31 participants had slight, 19 had mild, and three had moderate hearing loss in the left ear. Five of the participants were using hearing aids. Seventy-six participants had normal hearing, 28 had slight, 17 had mild, three had moderate, and one had moderately severe hearing loss in the right ear. Participant data about the PTA (0.5–4 KHz), better ear PTA, worse ear PTA (WEPTA), tinnitus duration, tinnitus loudness (SL), tinnitus frequency, minimal masking level, residual inhibition, and tinnitus site are given in Table 1.

The mean of the Tr-ITI total score was 27.88±7.0 (min =8, max =39). The mean of each item and the average of the total items are given in Figure 1. The annoyance caused by tinnitus

Table 1. Participants' information about demographic, tinnitus, and hearing status

		Participants (n=125)
Age (year)	Mean ± SD	49±1.1
Sex (M/F)	n	66/69
Hearing loss (NH/HL)	n	72/53
Right Ear PTA (dB HL)	Mean ± SD	20±11.5
Left Ear PTA (dB HL)	Mean ± SD	19.5±10.7
Better Ear PTA (dB HL)	Mean ± SD, (min-max)	17.1±9.7 (0–55)
Worse Ear PTA (dB HL)	Mean ± SD, (min-max)	21.9±12.1 (0–65)
Tinnitus duration (month)	Mean ± SD	13±1.2
Tinnitus duration		
3–6 months	n - %	40–32%
6 months–1year		15–12%
1–2 years		15–12%
More than 2 years		55–44%
Tinnitus loudness (SL)	Mean ± SD	34.6±27.7
Tinnitus frequency (KHz)	Mean ± SD	8.2±3.3
MML (SL)	Mean ± SD	7.9±4.4
Residual inhibition		
Complete (C)	n	75 (C), 40 (P), 10 (N)
Partial (P)		
No (N)		
Tinnitus site [Right (R), Left (L), Bilateral (B)]	n	45R, 43L, 37B

M: Male, F: Female, NH: Normal hearing HL: Hearing loss, SL: Sensation level, MML: Minimal masking level, SD: Standard deviation, min-max: Minimum-maximum

and the negative effects of tinnitus on enjoyment of life were the areas that individuals complained about the most.

The mean score of Tr-ITI was 27.8±7.7 (min =8, max =39) for females, and 28.593±6.4 (min =11, max =39) for males. There were no statistical differences between the mean score of males and females (Mann–Whitney U test, p=0.585). There were no correlations between tinnitus duration, gender, age, and total Tr-ITI score (Spearman's correlation test p>0.05). Likewise, no statistically significant correlations were found between the Tr-ITI score and the BEPTA and WEPTA (p>0.05).

The mean of the THI was 40.31±25.2 (min =6, max =100) which indicates level three tinnitus severity.

Construct Validity Results

Before the CFA, the suitability of the data for factor analysis and the adequacy of the sample was evaluated with Bartlett's sphericity test and KMO test. Bartlett's test of sphericity was $\chi 2$=604.774 (p=0.00) and KMO measure of sample adequacy was 0.899.

EFA showed that Tr-ITI had a single-factor structure in eight items in accordance with the original structure of the inventory. The factor structure of the 8-item Tr-ITI was tested with CFA. The results obtained with CFA and the path diagram are given in Figure 1. As seen in Figure 2, each item of the unidimensional inventory was meaningful and sufficient to explain the dimension. Factor loadings of items are shown in Table 2. These findings showed that TR-ITI is a unifactorial scale as is the original version.

The correlation between THI and Tr-ITI was moderate (Spearman's rho r=-0.620 p=0.00), which is the indicator of convergent validity (23).

The goodness of fit indexes of Tr-ITI and thresholds for acceptable and good fit are given in Table 3. Analysis showed that the indexes of the TR-ITI values met the threshold for a good fit.

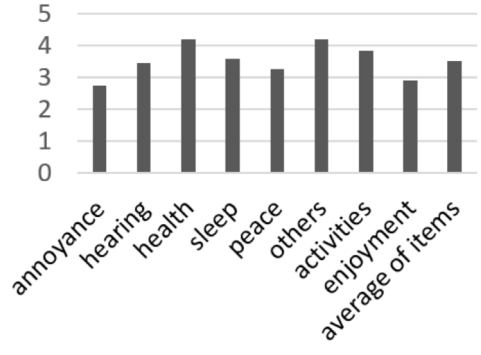

Figure 1. Means of Tr-ITI items
Tr-ITI: Turkish version of the International Tinnitus Inventory

Reliability Results

The responses given to the eight items by the participants with tinnitus and Cronbach's alpha were used to assess internal consistency. Cronbach's alpha was 0.909, which means high internal consistency. Item reliability was examined with item analysis, the correlation between the items was analyzed, and their consistency was studied. As seen in Table 4, there is a high positive correlation between items; the correlation coefficient was not below 0.30 in any of the items. These findings showed that the items in the Tr-ITI were interrelated and that no item should be removed. The highest correlation was found between "others" and "activities" items (r=0.786), and the lowest correlation was between "others" and "annoyance" items.

As a result, when Cronbach's alpha and correlation coefficients between items and the items analysis results were interpreted together, it was revealed that the Tr-ITI had a high degree of reliability. Table 5 shows that removing any item from the inventory did not increase the mean and Cronbach's alpha coefficient.

For test reliability, TR-ITI was completed for a second time by 50 subjects after a 15-day interval and total score consistency between measurements was found high (Pearson correlation test r=0.993, p=0.00).

Discussion

Tinnitus is a subjective phenomenon that is difficult to measure via evidence-based assessment. Self-report scales are indispensable tools in determining the severity of tinnitus and the domain of life it affects. Tinnitus affects life in different domains. Sleep problems, emotional distress,

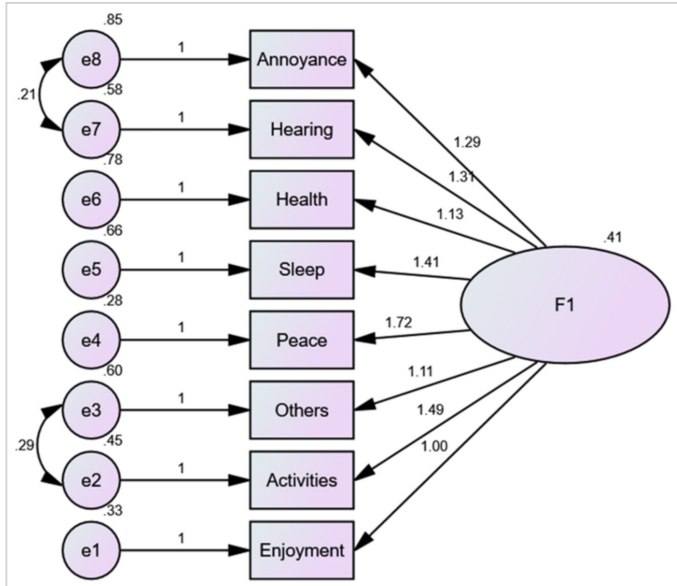

Figure 2. Unidimensional structural model for the Tr-ITI
Tr-ITI: Turkish version of the International Tinnitus Inventory

concentration difficulties, and social problems are the areas of tinnitus that most affect daily life. For effective counseling and therapy, identifying the primary complaints from tinnitus is crucial. Literature shows numerous scales and indexes for measuring tinnitus severity. The ITI is one of the short and easily applicable inventories for a tinnitus evaluation. It is valuable for the quick assessment of the most commonly reported tinnitus complaints (18).

Our study showed TR-ITI to be of a unifactorial structure similar to the original version of the inventory (Appendix). The findings suggest that the Tr-ITI has very high internal consistency reliability (Cronbach's alpha coefficients =0.909). The internal consistency reliability of the Tr-ITI is similar to those of the English (Chronbach's alpha coefficients =0.91) and the French (Chronbach's alpha coefficients =0.87) validations of inventory (18). As seen in Table 5, Cronbach's

Table 2. The Tr-ITI items and factor loadings

Item	Items in Turkish	Factor loadings
Item 1 (Annoyance): Think about your tinnitus over the past two weeks. On an average day, how often have you found it annoying?	Item 1: Son iki hafta içindeki çınlamanızı düşününün. Ortalama bir günde hangi sıklıkta sinir bozucu olduğunu düşündünüz?	0.667
Item 2 (Hearing): Think about the situation where you most wanted to hear. Over the past two weeks, how much difficulty has the tinnitus caused in that situation?	Item 2: İşitmenizin en iyi olmasını istediğiniz durumu düşünün: Son iki hafta içinde, o durumda çınlamanız ne kadar zorluğa neden oldu?	0.738
Item (Health) 3: How much has your tinnitus caused or aggravated other health problems?	Item 3: Çınlamanız başka sağlık sorunlarına neden oldu mu ya da diğer sağlık sorunlarınızı artırdı mı?	0.630
Item 4 (Sleep): Over the past two weeks, how much has your tinnitus affected your sleep?	Item 4: Son iki hafta içinde, çınlamanız uykunuzu ne kadar etkiledi?	0.741
Item 5 (Peace): Over the past two weeks, how much has your tinnitus affected your peace of mind?	Item 5: Son iki hafta içinde, çınlamanız iç huzurunuzu ne kadar etkiledi?	0.900
Item 6 (Others): Over the past two weeks, how much do you think your tinnitus has affected other people?	Item 6: Son iki hafta içinde çınlamanızın diğer insanları ne kadar etkilediğini düşünüyorsunuz?	0.673
Item 7 (Activities): Overall, how much has your tinnitus affected the things you can do?	Item 7: Genel olarak, çınlamanız yapabileceğiniz şeyleri ne kadar etkiledi?	0.819
Item 8 (Enjoyment): Considering everything, how much has your tinnitus changed your enjoyment of life?	Item 8: Her şey göz önüne alındığında, çınlamanız yaşamdan aldığınız zevki ne kadar değiştirdi?	0.743

Tr-ITI: Turkish version of the International Tinnitus Inventory

Table 3. Comparison of standard adaptation for good fit and acceptable fit index parameters with Tr-ITI

	χ^2/d.f.	RMSA	GFI	AGFI	NFI	CFI	IFI
Thresholds for acceptable fit	2≤ χ2/SD ≤3	0.05≤ RMSEA ≤0.08	0.90≤ GFI ≤0.95	0.85≤ AGFI ≤0.90	0.90≤ NFI ≤0.95	0.90≤ CFI ≤0.95	0.90≤ IFI ≤0.95
Thresholds for good fit	0≤ χ2/SD ≤2	0.00≤ RMSEA ≤0.05	0.95≤ GFI ≤1.00	0.90≤ AGFI ≤1.00	0.95≤ NFI ≤1.00	0.95≤ CFI ≤1.00	0.95≤ IFI ≤1.00
Measurement model (Tr-ITI)	**1.258**	**0.46**	**0.956**	**0.912**	**0.964**	**0.992**	**0.992**

χ2 /d.f.: Chi-square divided by the degrees of freedom, GFI: Goodness of fit index, AGFI: Adjusted GFI, CFI: Comparative fit index, RMSEA: Root mean square error of approximation, CFI: Comparative Fit Index, IFI: Incremental Fit Index, SD: Standard deviation, Tr-ITI: Turkish version of the International Tinnitus Inventory

Table 4. Item correlation matrix of Tr-ITI

Item	Item 1: Annoyance	Item 2: Hearing	Item 3: Health	Item 4: Sleep	Item 5: Peace	Item 6: Others	Item 7: Activities	Item 8: Enjoyment
Item 1: Annoyance	1.000							
Item 2: Hearing	0.643	1.000						
Item 3: Health	0.433	0.523	1.000					
Item 4: Sleep	0.513	0.586	0.454	1.000				
Item 5: Peace	0.625	0.662	0.525	0.671	1.000			
Item 6: Others	0.383	0.497	0.553	0.453	0.596	1.000		
Item 7: Activities	0.504	0.600	0.587	0.614	0.722	0.786	1.000	
Item 8: Enjoyment	0.469	0.488	0.436	0.503	0.705	0.525	0.626	1.000

Tr-ITI: Turkish version of the International Tinnitus Inventory

Table 5. Change of Cronbach's alpha value for items in the Tr-ITI

	Scale mean if item deleted	Scale variance if item deleted	Corrected item-total correlation	Cronbach's alpha if item deleted
Annoyance	25.47	39.025	0.642	0.904
Hearing	24.77	38.905	0.732	0.895
Health	24.02	40.129	0.627	0.904
Sleep	24.63	38.638	0.687	0.899
Peace	24.95	36.772	0.829	0.886
Others	24.02	40.298	0.681	0.900
Activities	24.39	37.531	0.812	0.888

Tr-ITI: Turkish version of the International Tinnitus Inventory

alpha coefficient decreased after removing each of the eight ITI items from the inventory construct. Moreover, Table 4 shows that inter-item correlations were high; these indicate that each item contributes to Tr-ITI. For this reason, the number of items in the Turkish version was not changed, and the study was completed without removing any items. The positive correlations between inventory items range between 0.14 and 0.68 in the French version and between 0.32 and 0.75 in the English version of the ITI. Our correlations between items range between 0.3 and 0.7, findings were similar to those of the French and English versions of the inventory. The highest correlation seen between "others" and "activities" items come to mean that tinnitus negatively affects social life. In our study, the annoyance caused by tinnitus and the decrease in the enjoyment of life were the most common complaints of individuals. The item related to the annoyance caused by tinnitus was also the item with the worst average score in the English and French versions. Tinnitus distress or annoyance is the common patient-reported complaint, so questions about these issues appear on nearly all self-report tinnitus scales (10, 24, 25).

The ITI, compared to other tinnitus-related questionnaires, contains few items. When we studied the tools for tinnitus measurement, we saw that widely used questionnaires and scales have a large number of items, for example the THI and the Tinnitus Functional Index have 25 items, the Tinnitus Questionnaire has 52 items, the Tinnitus Handicap Questionnaire has 27 items, and the Tinnitus Reaction Questionnaire has 26 items (11-15). Among these tools, the ITI stands out in its shortness, easy application, and usefulness in determining the symptoms of tinnitus quickly. Tinnitus is a complex auditory symptom and is comorbid with a lot of diseases and health conditions (like sleep problems, psychiatric illness, etc.) and needs to be evaluated in many ways (24-27). To evaluate tinnitus and these conditions, many assessment questionnaires and scales are used in the initial tinnitus assessment and follow-up period. This causes the patient to get bored while applying the scales, perhaps not being able to complete the forms carefully and creating doubts about the reliability and accuracy of the answers.

Our study found that the mean score of Tr-ITI was 27.88±7.0, and the study of the original version of ITI was 31.6. The mean THI score of our participants was 40.31±25.2 (level three tinnitus severity) and there was a strong correlation between THI and Tr-ITI scores. THI is the most widely used scale for assessing tinnitus severity and the Tr-ITI score showed high consistency with THI. The Tr-ITI could be used instead of THI for tinnitus measurement, especially in the initial interview of tinnitus evaluation in busy ENT and audiology clinics. ITI is a robust questionnaire and easy to interpret (18). The literature shows that ITI is frequently used in the evaluation of tinnitus, especially in Ménière's disease patients (28-32).

Our study evaluated the validity of the Tr-ITI using the path diagram and the goodness of fit indexes. The model of the Tr-ITI data showed that the fitness degree index of the structural model is significant (p=0.00). As shown in Table 3, all fit index parameters of the Tr-ITI are between the thresholds for a good fit. Furthermore, the Tr-ITI has excellent test-retest reliability, meaning the inventory is consistent and stable over time. No retesting has been performed in the English and French versions. Researchers project this in future studies (18).

This study also investigated the possible correlations between the participant's age, gender, tinnitus duration hearing level, and the total score of the inventory. In the French and English versions, there was no correlation between age, gender, and the ITI total score. However, in this study, a very weak negative correlation was found between ITI total score and tinnitus duration and best ear hearing level. The tinnitus duration of their patients was one month to 57 years, whereas in our study, it was 13±1.2 months, it is probable that there was no correlation in our study because of this difference. The PTA of our participants was at a slight hearing loss level. Since we did not have many patients with hearing loss, it was thought that there was no relationship between tinnitus and hearing problems. Considering the theories of tinnitus pathophysiology, hearing loss is one of the important risk factors for developing tinnitus, but it is known that tinnitus is frequently seen in individuals without hearing loss.

There are many parameters other than hearing loss that affect the severity and continuity of tinnitus (27, 33, 34).

Self-report tinnitus questionnaires ask about particular difficulties in concentration, sleeping, coping, social, emotional well-being, and general health. The purpose of these questionnaires is to determine tinnitus severity and most particularly complaints of tinnitus (35). Then, it is aimed to help the patient by measuring counseling, therapy planning, and therapy outcomes. Tr-ITI is a valid and reliable inventory that can be used by relevant specialists such as audiologists, psychologists, and ENT specialists, useful in quickly obtaining information about complaints caused by tinnitus, and easy to implement and interpret.

Conclusion

TR-ITI is a valid and reliable scale with a high-reliability coefficient and good compliance values that can be used in Turkish for research and clinical purposes.

It is an inventory that can be used easily, especially in busy clinics in terms of easy application and time saving.

Ethics Committee Approval: The research protocol was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee with project no. GO 18/1106 (decision no: GO 18/1106-31, date: 27.11.2018).

Informed Consent: The informed consent form was signed by all participants in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.İ.Ş.K., S.A., Design: G.İ.Ş.K., S.A., Data Collection and/or Processing: G.İ.Ş.K., G.B.Ç., Analysis and/or Interpretation: G.İ.Ş.K., G.B.Ç., Literature Search: G.İ.Ş.K., G.B.Ç., Writing: G.İ.Ş.K., S.A.

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

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Main Points

- Tinnitus negatively affects life in many areas within a wide range from sleep to concentration problems and from emotional to social problems. However, these effects are independent of the psychoacoustic character of tinnitus.
- The effect of tinnitus on quality of life and the effectiveness of therapy/treatment are determined by self-report scales and questionnaires.
- Turkish version of the International Tinnitus Inventory is a short, timesaving, valid and reliable screening scale that can be easily applied in audiology and ENT clinics and evaluates all domains of tinnitus.

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Appendix.

1. Son iki hafta içindeki çınlamanızı düşününün. Ortalama bir günde hangi sıklıkta sinir bozucu olduğunu düşündünüz?

Her zaman	Çoğunlukla	Bazen	Ara sıra	Asla

2. İşitmenizin en iyi olmasını istediğiniz durumu düşünün: Son iki hafta içinde, o durumda çınlamanız ne kadar zorluğa neden oldu.

Çok fazla	Oldukça fazla	Orta derecede	Biraz	Hiç

3. Çınlamanız başka sağlık sorunlarına neden oldu mu ya da diğer sağlık sorunlarınızı artırdı mı?

Çok fazla	Oldukça fazla	Orta derecede	Biraz	Hiç

4. Son iki hafta içinde, çınlamanız uykunuzu ne kadar etkiledi?

Çok fazla	Oldukça fazla	Orta derecede	Biraz	Hiç

5. Son iki hafta içinde, çınlamanız iç huzurunuzu ne kadar etkiledi?

Çok fazla	Oldukça fazla	Orta derecede	Biraz	Hiç

6. Son iki hafta içinde çınlamanızın diğer insanları ne kadar etkilediğini düşünüyorsunuz?

Çok fazla	Oldukça fazla	Orta derecede	Biraz	Hiç

7. Genel olarak, çınlamanız yapabileceğiniz şeyleri ne kadar etkiledi?

Çok fazla	Oldukça fazla	Orta derecede	Biraz	Hiç

8. Her şey göz önüne alındığında, çınlamanız yaşamdan aldığınız zevki ne kadar değiştirdi?

Çok daha kötüleştirdi	Oldukça çok kötüleştirdi	Biraz kötüleştirdi	Hiç kötüleştirmedi	Daha da iyileştirdi

Evaluation of Thyroidectomy Results Performed at a Tertiary Academic Center

Original Investigation

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Abstract

Objective: The aim of the study was to retrospectively analyze the patients who underwent thyroidectomy at a tertiary academic center regarding their surgical indications, histopathological diagnosis, and surgical complications.

Methods: The study included a total of 739 consecutive patients who underwent lobectomy, total thyroidectomy, or completion thyroidectomy performed under intraoperative nerve monitoring (IONM) at the Department of Otorhinolaryngology-Head and Neck Surgery of Dokuz Eylül University between January 2009 and December 2019. Demographic data of the patients, preoperative clinicopathological characteristics, postoperative complications, characteristics of surgery and histopathological results were evaluated.

Results: There were 619 patients in the primary surgery and 120 patients in the revision surgery groups. Indications for surgery were suspicion of malignancy in 486, multinodular goiter in 214, and hyperthyroidism in 39 patients. Final histopathological evaluation of specimens revealed malignancy in a total of 507 (68.6%) patients. Rates of transient and permanent hypocalcemia were 7.3% (54/739) and 2.2% (16/739) in the whole group, while this was 6.6% (41/619) and 1.5% (9/619), respectively, among primary total thyroidectomy patients. There were 61 (8.3%) patients with transient recurrent laryngeal nerve (RLN) paralysis (unilateral in 60 patients, bilateral in one patient) and five (0.7%) patients with permanent unilateral RLN paralysis as postoperative complications. Rates for postoperative hematoma, seroma, wound infection and chylous fistula were 2.2%, 3.7%, 0.1%, and 0.5%, respectively.

Conclusion: Our results support the safety of thyroid surgery performed under IONM in tertiary academic centers. Every institution should document and share its own results to properly inform its patients preoperatively.

Keywords: Thyroidectomy, hypocalcemia, vocal cord paralysis, recurrent laryngeal nerve

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Introduction

Thyroid surgeries are considered safe surgeries with low complication rates, however, different complications such as hypocalcemia, recurrent laryngeal nerve (RLN) paralysis, and hemorrhage can be occurred after thyroidectomy. The most common complication after bilateral total thyroidectomy is hypocalcemia. In the literature, transient hypocalcemia has been reported between 1.36–50.0%, and

permanent hypocalcemia between 0.0–3.0% (1, 2). RLN injury is the main cause of morbidity that affects the quality of life after thyroidectomy. The incidence of transient RLN injury has been reported as 0.36–30.00%, and the incidence of permanent RLN injury as 0.5–5.2% (3-6). The incidence of postoperative hematoma has been reported between 0.0–6.5%, and this complication is a rare but a serious one that usually occurs within the first six hours postoperatively (7, 8). Chylous fistula is a rare complication usually seen in patients who undergo simultaneous lateral neck dissection (9). The incidence of surgical wound infection was reported as 0.4% (10).

The aim of the presented study was to retrospectively evaluate the patients who underwent thyroidectomy in our clinic regarding their surgical indications, histopathological diagnosis, and surgical complications.

Methods

All consecutive patients operated on by the Department of Otorhinolaryngology-Head and Neck Surgery of Dokuz Eylül University between January 2009 and December 2019 with the indication of total or completion thyroidectomy were included in the study. Intraoperative nerve monitoring (IONM) was used routinely in all patients. Patients' age, gender, indications for surgery, ultrasonography results, thyroid autoantibody results, vocal cord movements before and in the early and late periods after surgery, surgical characteristics (total or completion thyroidectomy, presence of neck dissection, drain placement), pathology results, serum calcium (Ca) and parathormone levels measured before and during the first week and in the later periods after surgery, postoperative complications and their time of occurrence were recorded in the data recording form.

For serum Ca evaluations, patients with a Ca value below 8.0 mg/dL in a single measurement after surgery were considered hypocalcemic. Hypocalcemia lasting shorter than 12 months was defined as transient, and hypocalcemia lasting longer than 12 months was defined as permanent hypocalcemia. Analyses for transient and permanent hypocalcemia were done for the whole group as well as the primary total thyroidectomy group with the exclusion of hemithyroidectomy patients and patients who underwent parathyroid adenoma surgery simultaneously with total thyroidectomy.

During IONM, a response less than 100 mV for 1 milliampere stimulus given to the RLN during the operation was considered a loss of signal. Vocal cord paralysis lasting longer than 12 months was defined as permanent vocal cord paralysis, and vocal cord paralysis lasting less than 12 months was defined as temporary vocal cord paralysis. Since the written records of the vocal cord examination in the fiberoptic nasal endoscopy routinely performed before and after the surgery were fully accessible in 737 of 739 patients, the rates of vocal cord paralysis were evaluated on 737 patients.

Our retrospective study was approved by Dokuz Eylül University Non-Interventional Research Ethics Committee with decision number 2021/02-44 (date: 18.01.2021) but informed consent was not obtained from the patients because of the anonymous and retrospective design of the study.

Statistical Analysis

In data analysis, frequencies and percentages are presented as descriptors. Analytical frequencies were compared with the chi-square test, a p-value less than 0.05 was accepted as statistically significant. Statistical analyses were done with the IBM SPSS 24.0 program (Armonk, NY: IBM Corp).

Results

There were 739 consecutive patients who underwent lobectomy, total thyroidectomy, or completion thyroidectomy. Of these patients, 554 (75.0%) were female and 185 (25.0%) were male. The mean age of the patients was 47.16±13.50 years.

There were 619 patients in the primary surgery and 120 patients in the revision surgery groups. Indications for surgery were suspicion of malignancy in 448, multinodular goiter (MNG) in 132, and hyperthyroidism in 39 patients in the primary surgery group, while there were 38 patients with suspicion of malignancy and 82 patients with MNG and compression symptoms in the revision thyroid surgery group.

When evaluated in terms of retrosternal extension, there were 67 (9.1%) patients with retrosternal extension and 672 (90.9%) patients without. A total of 527 (71.3%) patients underwent total thyroidectomy, 120 (16.2%) underwent completion thyroidectomy, and 92 (12.4%) underwent hemithyroidectomy. Thyroidectomy was performed without neck dissection in 618 (83.6%) of the patients. In addition to thyroidectomy, central neck dissection was performed in 56 (7.6%) patients, and central and lateral neck dissection was performed in 63 (8.5%) patients. Lateral neck dissection was performed in two (0.3%) patients with a history of thyroid surgery and central neck dissection. Drains were used during the operation in 233 (31.5%) of the cases, while drains were not used in 506 (68.5%) cases.

Final histopathological evaluation of thyroidectomy specimens revealed malignancy in 507 (68.6%) patients. In the malignancy group, 457 (90.1%) patients had early-stage (T1 and T2), and 50 (9.9%) patients had late-stage (T3 and T4) tumors. Papillary carcinoma was identified in 465 (91.7%) patients with malignant pathology, follicular carcinoma in 18 (3.6%) patients, and medullary carcinoma in 10 (2.0%) patients. The remaining 14 (2.7%) patients had

different types of rare thyroid carcinomas such as Hurthle cell carcinoma, mixed type carcinoma, poorly differentiated carcinoma, and anaplastic carcinoma.

In the evaluations made in terms of hypocalcemia, a total of 70 (9.5%) hypocalcemic cases were found in the total group of 739 cases whose serum Ca levels fell below 8.0 mg/dL in a single measurement after surgery. Among all patients, transient hypocalcemia developed in 54 (7.3%) cases and permanent hypocalcemia in 16 (2.2%) cases. After the exclusion of 115 patients who underwent hemithyroidectomy and parathyroid adenoma excision in addition to thyroid surgery, evaluation for hypocalcemia was also performed for primary total thyroidectomy (n=502) and completion thyroidectomy (n=120) patients. Rates of transient and permanent hypocalcemia were 8.2% (41/502) and 1.8% (9/502), respectively, for primary total thyroidectomy patients; and 10.8% (13/120) and 5.8% (7/120), respectively, for completion thyroidectomy patients.

Of the 739 patients 25 (3.4%) had pre-operative vocal cord paralysis. After the exclusion of pre-operative paralytic nerves, there were 1300 pre-operatively functioning nerves at risk (NAR), of which 1046 were in 527 total thyroidectomy patients, 90 in 92 hemithyroidectomy patients, and 164 RLN in 120 completion thyroidectomy patients. In the routine flexible endoscopic examination performed during the follow-up period postoperative vocal cord paralysis was detected in 68 patients. In two of these patients, the RLNs had to be sacrificed due to invasion by thyroid malignancy and were not classified as a surgical complication. Therefore, a total of 66 patients (8.9%) had vocal cord paralysis as a complication of the surgery with right vocal cord paralysis in 31 (4.1%) patients, left vocal cord paralysis in 34 (4.6%) patients, and bilateral vocal cord paralysis in one patient. Vocal cord paralysis was found to be temporary in 61 (8.3%) and permanent in five (0.7%) patients. In the evaluation made in terms of NAR, 67 (5.2%) of 1300 RLNs had RLN paralysis as a surgical complication in the early postoperative period. Temporary and permanent RLN paralysis rates were found in 62 (4.8%) and five (0.4%) NAR.

In the postoperative follow-up, hematoma occurred in 16 (2.2%) patients, seroma in 27 (3.7%) patients, chylous fistula in four (0.5%) patients. There was one wound infection (0.1%) on the seventh postoperative day, and the patient was hospitalized and treated for a week.

Transient hypoglossal nerve injury was observed in one (0.1%) patient who underwent completion total thyroidectomy and simultaneous central and lateral neck dissection.

Hematoma occurred in 11 (68.7%) of 16 patients within the first 24 hours and after 24 hours in the remaining five (31.3%) patients. Eight of these patients (50%) underwent neck exploration due to hematoma, while eight patients (50%) were managed with conservative follow-up.

In the evaluation of hematoma development and drain placement, 10 of 233 patients (4.3%) with drains and six of 506 patients (1.2%) without drains had hematoma (p=0.007). Although hematoma was observed more often in patients with drains, it was also found that drain placement was statistically significantly higher in surgeries with a high risk of complications such as revision thyroid surgery, retrosternal thyroid extension, advanced tumor stage, and performance of simultaneous neck dissection (Table 1).

Discussion

Indications for thyroidectomy are generally classified as malignancy risk, local compression symptoms, and hyperthyroidism (11). Indications for surgery were similar in our study, namely, suspicion of malignancy in 448, MNG in 132, and hyperthyroidism in 39 patients in the primary surgery group; and suspicion of malignancy in 38 patients and MNG and compression symptoms in 82 patients in the revision thyroid surgery group.

The most common thyroid cancer is papillary thyroid cancer (>88%), followed by follicular thyroid cancer (8%) and Hurthle cell carcinoma (2.3%). The incidence of medullary thyroid cancer which originates from the parafollicular cells is approximately 2% (11). In our patient sample of 507 patients with malignant pathology in their specimens, 465 (91.7%) had papillary carcinoma, 18 (3.6%) had follicular carcinoma,

Table 1. Patient groups with and without drains

	Drain placement		
	Yes number (%)*	No number (%)*	p-value**
History of thyroid surgery			
Yes	63 (52.5)	57 (47.5)	**<0.05**
No	170 (27.5)	449 (72.5)	
Retrosternal extension			
Yes	45 (67.2)	22 (32.8)	**<0.05**
No	188 (28.0)	484 (72.0)	
Malignancy			
Yes	69 (29.7)	163 (70.3)	0.479
No	164 (32.3)	343 (67.7)	
T-stage			
Stage 1-2	128 (28.0)	329 (72.0)	**<0.05**
Stage 3-4	36 (72.0)	14 (28.0)	
Neck dissection			
Yes	102 (84.3)	19 (15.7)	**<0.05**
No	131 (21.2)	487 (78.8)	

*Row percentages are given. **P-values were calculated with the Pearson's chi-square test

10 (2.0%) had medullary carcinoma while 14 (2.7%) patients had rare thyroid carcinomas such as Hurthle cell carcinoma, mixed type carcinoma, poorly differentiated carcinoma, and anaplastic carcinoma. Papillary thyroid cancer and medullary thyroid cancer rates were comparable to those reported in the literature, whereas follicular thyroid cancer was found at a lower rate.

The most common complication after total thyroidectomy is hypocalcemia. Its incidence has been reported between 1–50% after total thyroidectomy (1, 12-14). Cho et al. (1) found the rate of transient hypocalcemia as 19–38% and the rate of permanent hypocalcemia as 0–3% after thyroidectomy. In their study, Tutar et al. (15) found the rate of temporary hypocalcemia after thyroidectomy as 15%.

In our study, a single serum Ca level less than 8.0 mg/dL, regardless of whether or not the patients were symptomatic, was defined as hypocalcemia. In our series, transient hypocalcemia was reported in 54 patients, and permanent hypocalcemia was reported in 16 patients after surgery. Our rates of temporary and permanent hypocalcemia were 7.3% and 2.2%, respectively, in the whole series of 739 cases. In subgroup analyses, rates of transient and permanent hypocalcemia were 8.2% (41/502) and 1.8% (9/502), respectively, for primary total thyroidectomy patients, and 10.8% (13/120) and 5.8% (7/120), respectively, for completion thyroidectomy patients. Although our results for hypocalcemia rates are among the lower rates given in the literature, it was observed that patients in the completion thyroidectomy group had more than a threefold risk of permanent hypocalcemia when compared to the patients in the primary thyroidectomy group (5).

In the literature, the incidence of temporary and permanent paralysis of RLN after thyroidectomy has been reported as 0.36–30.00% and 0.5–5.2%, respectively (4-6, 16, 17). In their study including 1547 patients and 2527 RLNs at risk, Dhillon et al. (4) reported that RLN paralysis developed in 73 (2.9%) RLNs, and paralysis was permanent in nine (0.4%) patients. The study by Aspinall et al. (18), in which 218 surgeons were evaluated according to their annual thyroidectomy volumes, showed that the risk of postoperative hypocalcemia and vocal cord paralysis was significantly lower among the cases of surgeons with high annual operating volumes. In our study, we found a total of 1300 RLNs to be at risk, including 1046 in 527 total thyroidectomy patients, 90 in 92 hemithyroidectomy patients, and 164 RLN in 120 completion thyroidectomy patients. Temporary vocal cord paralysis was detected in 61 patients and permanent vocal cord paralysis in five patients. In the evaluation of NAR, 62 of the 1300 RLNs had transient, and five had permanent RLN paralysis. Temporary and permanent vocal cord paralysis rates were 8.3% and 0.7% on a patient basis, and 4.8% and 0.4% on a NAR basis. Our paralysis rates are among the low incidence rates reported in the literature. The high number of thyroid surgeries performed in our clinic and the routine use of IONM during surgeries are deemed to have contributed to the low rates of temporary and permanent vocal cord paralysis in our series.

In the literature, the incidence of hematoma after thyroid surgery has been reported between 0.43% and 6.54%. Risk factors that can lead to hematoma are advanced age, male gender, revision surgery, hypertension, neck dissection, bilateral surgery, increased thyroid gland volume, use of antithrombotic drugs, and autoimmune thyroiditis (19, 20). In our study, postoperative hematoma occurred in 16 patients and the rate of hematoma was calculated as 2.2%. There are studies in the literature supporting that the use of drains during operation is not associated with lower incidences of postoperative hematoma and prolongs the hospitalization period of patients (19, 20). In our study, hematoma was occurred in 4.3% of the cases in which a drain was placed, and in 1.2% of the cases in which a drain was not placed, and it was found that hematoma occurrence was statistically more common in cases in which a drain was placed ($p<0.05$). When further factors were evaluated, however, the higher rate of hematoma in cases with drain insertion was attributed to higher-risk surgeries such as revision surgery, retrosternal extension, advanced-stage tumor surgery, and performance simultaneous neck dissection (Table 1).

According to the literature, the reported incidence of seroma after thyroid surgery ranges from 1.3% to 7.0%. While there are studies showing advanced age and obesity as risk factors for the development of seroma, there are also studies showing that gender and the use of a drain are not associated with seroma (21, 22). In our study, seroma was observed in 27 (3.7%) patients, and this rate is consistent with the literature data.

Chylous fistula is a rare complication usually occurred in patients with simultaneous lateral neck dissection or with an intrathoracic thyroid nodule. If it occurs, conservative treatment is recommended as the first approach. However, when a complicated or high-flow fistula is observed, surgical ligation of the duct is required (9, 23). Polistena et al. (9) in their study involving 13,224 cases, found chylous fistula in 0.01% of the cases and treatment was conservative in 30% of patients. In our study, chylous fistula occurred in four (0.5%) cases. Two patients required neck exploration due to chylous fistula, while the chylous fistulas of two patients were treated conservatively with a low-fat diet. In our study, 50% of the patients who occurred chylous fistula were treated conservatively, an approach similar to those in the literature.

The incidence of wound infection after thyroidectomy has been reported as 0.4%. Advanced age, male gender, smoking and alcohol use, and obesity are among the risk factors (10, 24). Elfenbein et al. (10) found the rate of

wound infection as 0.36% in their study including 49,326 cases who underwent thyroidectomy. In our study, there was one wound infection (0.1%) on the seventh postoperative day, and the patient was hospitalized and treated for a week.

Conclusion

Surgical indications, pathology results, and complication rates in our study are consistent with the results given in the literature and support that thyroid surgeries performed with IONM in experienced centers are among safe surgeries with low complication rates. However, although the complication rates associated with thyroidectomy are low in experienced centers, institutions should document and share their own results to properly inform their patients.

Ethics Committee Approval: Our retrospective study was approved by Dokuz Eylül University Non-Interventional Research Ethics Committee with decision number 2021/02-44 (date: 18.01.2021).

Informed Consent: Informed consent was not obtained from the patients because of the anonymous and retrospective design of the study.

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Authorship Contributions

Surgical and Medical Practices: F.Y.E., E.D., M.G.D., S.S., A.Ö.İ., Concept: F.Y.E., A.Ö.İ., Design: F.Y.E., A.Ö.İ., Data Collection and/or Processing: F.Y.E., A.Ö.İ., Analysis and/or Interpretation: F.Y.E., P.K., A.Ö.İ., Literature Search: F.Y.E., A.Ö.İ., Writing: F.Y.E., A.Ö.İ.

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Main Points

- We aimed to retrospectively evaluate the patients who underwent thyroidectomy in our clinic regarding their surgical indications, histopathological diagnosis, and surgical complications.
- Thyroid surgeries performed with IONM in experienced centers are among safe surgeries with low complication rates.
- Institutions should document and share their own results to properly inform their patients.

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Effects of Cross-linked Hyaluronic Acid in a Rat Model of Vestibular and Cochlear Toxicity

Original Investigation

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Abstract

Objective: To investigate the effects of cross-linked hyaluronic acid (CLHA) in an experimental model of vestibulotoxicity and cochleotoxicity.

Methods: Twenty-eight female Wistar albino rats (200–250 g) were divided into four groups. Group A received 0.06 mL of 13.33 mg/mL gentamicin, Group B received 0.06 mL of CLHA, Group C received 0.03 mL of 26.66 mg/mL gentamicin and 0.03 mL CLHA, and Group D received 0.06 mL of 0.09% saline. All groups underwent auditory brainstem response testing at 4–32 kHz, signal-to-noise ratio of distortion product otoacoustic emission measurements at 1.5–8 kHz and vestibular tests on days 0,1,7,10. The rats were sacrificed, and their labyrinths were histologically assessed and scored.

Results: The hearing thresholds of Groups A and C were similar and significantly higher than those of the other groups at all frequencies, beginning from day 1. The vestibular and histological scores of Groups A and C were similar and significantly higher than those of the other groups from day 1. The audiological results, vestibular scores, and histological scores of Groups B and D were similar, except for a temporary middle ear effusion and hearing threshold shift in Group B. No significant deterioration was observed in the audiological, vestibular, and histological analyses of Groups B and D.

Conclusion: That both Group A and Group C similarly showed worsening audiological, vestibular, and histological tests suggests that CLHA did not alter the pharmacokinetics and histologic results of gentamicin.

Keywords: Gentamicin, hyaluronan, drug-related ototoxicity, hearing loss, audiology, vestibular function tests, animal research

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Introduction

The transtympanic administration of gentamicin is a well-known experimental model of combined vestibulotoxicity and cochleotoxicity. The dose and delivery protocol, the length of exposure, the middle ear volume, round window (RW)/oval window (OW) permeability, systemic diseases, window permeability modifiers and inner ear drug delivery systems may alter the toxicity of gentamicin (1-4). Hyaluronan (HA) is an endogenous glycosaminoglycan that structurally

participates in the various tissues of the human body, even in perilymph (5). However, it may alter the perilymphatic pharmacokinetics of an intratympanically administered drug via several mechanisms (1, 6, 7). In addition to its experimental and clinical use for inner ear drug delivery, the antibacterial, anti-adhesive, and regenerative properties of HA allow for its use in many otological applications such as middle ear packing, tympanic membrane repair, management of chronic otitis media and hearing preservation during cochlear implantation (8).

Cross-linked hyaluronic acid (CLHA) is a more stable type of HA that prevents rapid elimination of the natural liquid form (5). In previous studies, the effects of CLHA were examined only audiologically or histopathologically (9-12). This study aimed to examine the impact of CLHA on the inner ear in audiological, vestibular, and histopathological aspects in a gentamicin-induced cochleo-vestibulotoxicity model.

Methods

Animals

The study was approved by the local ethics committee (protocol date: 07/18/2018 and protocol number: 52/2018) of the Dokuz Eylül University Department of Scientific Research Projects of the Ministry of Health. Twenty-eight female Wistar albino rats weighing 200–250 g were used. They were bred and settled at a temperature of 20–25 °C with relative humidity and 12 hours of light and dark cycle in standard cages sized 50×80×100 cm. Standard pellets and tap water were supplied ad libitum. Three animals were placed in each cage.

Study Design and Intervention

This experimental study was conducted in March and April 2019. Twenty-eight rats with normal hearing and balance functions, according to the baseline audiological and vestibular assessment, were randomized into four groups to receive one of the investigational drugs intratympanically every day between 14:30 and 15:30 hours for seven days. Group A received only 0.06 mL of gentamicin at a concentration of 13.33 mg/mL (Genta, Ulagar Turkish Inc., İstanbul, Turkey), Group B received 0.06 mL of CLHA (PureRegen Gel Otol 2 mL, Bioregen Biomedical, Changzhou Co. Ltd.), Group C received 0.03 mL gentamicin at a concentration of 26.66 mg/mL and 0.03 mL CLHA, and Group D received 0.06 mL 0.09% saline. All rats were anesthetized by intraperitoneal injections (i. p.) of 50 mg/kg of ketamine hydrochloride (Ketalar 500 mg flk, Pfizer Company, USA) and 5 mg/kg of xylazine (Xylamed 5 mg/mL flk, Bimeda Animal Health Limited, Ireland) before intratympanic injections. Intratympanic injections were administered to the anteroinferior quadrant of the right tympanic membrane with a 20-gauge needle (B. Braun Venofix 20G, B. Braun Melsungen Medical Device Company, Germany) under otomicroscopy (Zeiss OPMI-1, Carl Zeiss AG, Germany), daily for a week.

Investigation of Cochlear and Vestibular Toxicity

The animals underwent vestibular and cochlear measurements on days 0, 1, 7, and 10 between 07:00 and 10:30 hours, and 11:00 and 14:30 hours, respectively. Cochlear toxicity assessment was done by measuring auditory brainstem responses (ABR) [Intelligent Hearing Systems Smart-EP l0 (lHS Corp, Miami, FL, USA)] and distortion product otoacoustic emission (DPOAE) (Otodynamics Echoport ILO-V6 Cochlear Emission Analyzer 5.61, Otodynamics, London, UK), on days 0 (before intratympanic injections), 1, 7, and 10. subdermal needle electrodes (Neuroline Subdermal, 12×0.5 mm, Ambu A/S, Malaysia) were used to record the ABRs. Tone-burst stimuli were presented at 4, 8, 16, 20, and 32 kHz, with a 1 ms rise-fall by a Blackman window envelope, in alternating polarity. Acoustic signals were recorded by bandpass filtering at 30–3000 Hz, and A/D was converted at a sampling rate of 25 kHz. The analysis time was set at 10 ms and the artifact rejection level at 31.00. ABR waves were obtained using 1000 stimuli presented at a rate of 37.1/s. DPOAE was measured using a neonatal probe. The f2/f1 ratio was maintained at 1.22. The levels of the stimulus were L1 (65 dB SPL) for f1 frequency and L2 (55 dB SPL) for f2 frequency. The baseline hearing condition of rats was measured with DPOAE and the signal-to-noise ratio was recorded at seven frequencies between 1500 and 8000 Hz. The vestibular test battery included tail-hanging, air-righting reflex, and swimming (13). The tail hanging test evaluated unilateral contraction and rotational movements of the rats attached to their tails with plastic plasters and suspended from a 50 cm high table for two minutes. The air-righting test measured the rats' ability to correct their posture when held on the back at a height of 30 cm for two minutes and subsequently dropped on a surface of soft textiles and foam. The swimming test was performed in a 30 cm diameter and 50 cm height cylindrical-shaped polyethylene pool filled with 30 cm tap water at a constant temperature of 37 °C. The deterioration in swimming quality and turning around the tail axis was observed for two minutes. After the swimming test, the grooming skill (ability to dry itself) was also observed for two minutes. Each animal was tested separately, and each test had a 10-minute interval during which the rats were allowed to rest in their cages. The rats were dried under a warm light source for 30 minutes after the swimming test. Behavioral tests were recorded using a camera (Eken 9HR 4 K Action Camera, Eken Electronics Ltd. Shenzhen, China) attached to a 15 cm height tripod located 30 cm away from the test field. The vestibular tests of the rats were videotaped and scored. Vestibular dysfunction score (VDS) refers to the sum of all vestibular assessment items (Table 1) (13, 14).

Table 1. Vestibular dysfunction score

	Score			
Variables	**0**	**1**	**2**	**3**
1- Tail hanging	No visible sign	Faint presence of the sign	Clear evidence of the sign	Maximum expression of the sign
2- Tail hanging tumbling	No visible sign	Faint presence of the sign	Clear evidence of the sign	Maximum expression of the sign
3- Air-righting reflex	Perfect preparation of the two front paws before reaching the ground	Mild impairment of the two front paws before reaching the ground	Severe impairment of the two front paws before reaching the ground	Absence of preparation for landing
4- Swimming turn to tail axis	No visible sign	Faint presence of the sign	Clear evidence of the sign	Maximum expression of the sign
5- Swimming quality	Normal swimming	Irregular swimming	Immobile floating	Underwater tumbling
6- Grooming after swimming	No visible sign	Faint presence of the sign	Clear evidence of the sign	Maximum expression of the sign

Explanatory table of the vestibular influence measurement method. In this table, the effect levels of drug-administered rats in 6 different categories were scored between 0 and 3. Rats with no effect got 0 points and those who were maximally affected got 3 points

Sacrification of Rats and Histopathological Examination

On the 10th day, after the final vestibular and cochlear evaluation, the rats were sacrificed using intracardiac ketamine hydrochloride (50 mg/kg) and xylazine hydrochloride (5 mg/kg). The tympanic bulla was resected. Tissues were fixed in 10% formalin solution for three days. Decalcification was accomplished using ethylenediaminetetraacetic acid solution at room temperature for a month. The decalcified tissues were embedded in paraffin blocks and 5 µm sections were taken with a rotary microtome (Leica, RM 2255, USA). The sections were stained with hematoxylin and eosin (H&E) (ab245880, Abcam, England) and evaluated under light microscopy (BH2, Olympos, Japan). Apoptosis was evaluated by TUNEL assay (the terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling) and activated Caspase-3 immunohistochemical staining. Chromatin concentration, nuclear fragmentation, shrinking of the cytoplasm, and formation of apoptotic bodies were considered as indicators of apoptosis (15).

The TUNEL Assay

The TUNEL assay was used to demonstrate DNA fragmentation. After deparaffinization, the sections were kept at first in Proteinase K (64220, Abcam, England) at 37 ˚C for 10 minutes and then in terminal deoxyribonucleotide transferase at 37 ˚C for 60 minutes. After converter peroxidase (POD) was applied, the sections were stained with diaminobenzidine (DAB, 1718096, Roche, Mannheim, Germany) and covered with entellan (Merck, Darmstadt, Germany) and background staining with Mayer hematoxylin (15).

Activated Caspase-3 Immunohistochemistry

After deparaffinization, the sections were heated in a microwave oven with 10 mM citrate buffer for 10 minutes. Tissues were limited with DakoPen (PAP pen, Dako Denmark APS, Denmark). Then, to inhibit endogenous tissue POD, 3% hydrogen peroxide was applied to the sections for five minutes. The sections, which were washed three times for five minutes with phosphate buffer solution, incubated with a blocking solution at room temperature for an hour and then incubated with anti-caspase 3 activated form (MAB10753, 1:100 dilution Sigma, Germany) at 4 ˚C without washing. A biotinylated secondary antibody (Histostain-Plus Broad Spectrum 85-Invıtrogene, Carlsbad, CA) and streptavidin were applied for 30 minutes, respectively. DAB was used to make the reaction visible. Ground staining was performed with Mayer hematoxylin. Sections, of which dehydration was carried out in graded alcohols, were covered with Entellan (15). The basilar membrane, spiral ganglion, cochlear nerve, stria vascularis, outer hairy cells, utricular and saccular macula, and apoptosis were evaluated and scored. The scores of these items represented the histological score (HS) (Table 2).

Statistical Analysis

The experimental outcomes were the ABR thresholds at individual frequencies, VDS, and HS. The Kolmogorov–Smirnov test was used for normal distribution analysis. Parametric quantitative variables were defined as mean ± standard deviation. For non-parametric quantitative variables, the median, minimum and maximum values were also calculated. Statistical analyses were done using SPSS version 22.0 (IBM Corp., Armonk, NY, USA) at a 95% confidence interval. One-way analysis of variance (ANOVA) and post-hoc Tukey-Kramer tests were used to compare the parametric quantitative variables between independent groups. The Kruskal–Wallis test and post-hoc Dunn–Bonferroni adjustment were used to compare the non-parametric quantitative variables between independent groups. The Friedman test and post-hoc Dunn–Bonferroni adjustment were used to assess the difference between non-

Table 2. Histomorphological score

	Score			
Variables	**0**	**1**	**2**	**3**
1- Spiral ganglion	No injury	Slight injury	Moderate injury	Severe injury, unrecognizable tissue morphology
2- Cochlear nerve	No injury	Slight injury	Moderate injury	Severe injury, unrecognizable tissue morphology
3- Stria vascularis	Absence of shrinkage of the intermediate cells	Slight shrinkage of the intermediate cells	Moderate shrinkage of the intermediate cells	Severe shrinkage of the intermediate cells
4- Outer hair cell (OHC)	Three OHCs with intact nuclei	Two OHCs with intact nuclei	One OHC with intact nuclei	No OHCs with intact nuclei
5- Utricular and Saccular macula	No injury	Slight injury	Moderate injury	Severe injury, unrecognizable tissue morphology
6- Apoptosis	No apoptotic cells	1–5 apoptotic cells	6–10 apoptotic cells	>10 apoptotic cells

Explanatory table of histological exposure measurement method. In this table, after the temporal dissection of drug-administered rats, cells in five different areas were examined for histological changes. While maximum exposure was 3 points, the areas that were not affected at all were scored as 0 points

parametric repeated measures of each group; $p<0.05$ was considered the minimum level of significance.

Blinding

Randomization and intratympanic injections were performed by a non-blinded investigator. Blinded authors performed intraperitoneal anesthesia, ABR and DPOAE recordings, vestibular assessment and scoring, sacrification, histological evaluation, and statistical analyses.

Results

None of the animals died and/or were excluded from the study during the experiment. Thus, the statistical analyses included all 28 animals.

Groups A and C showed significant cochleotoxicity at 4, 16, 32 kHz ABR frequencies in the first 24 hours ($p<0.05$). In Group A, the hearing thresholds were found to be progressively impaired and the worst hearing threshold was reached on the 10th day. Compared to the control group (Group D), significant differences were identified at all frequencies on days 1, 7 and 10. No significant differences were found between Groups A and C regarding the hearing status at any frequency measured on days 1, 7, and 10 ($p>0.05$) (Table 3).

In Group C, the hearing thresholds increased significantly at the 24th hour at 4 kHz (Mean ± SD; 26.43±2.4 dB $p<0.05$). Hearing deterioration was statistically significant at all frequencies on days 7 and 10 ($p<0.05$).

There were no significant differences between Groups B and D regarding the hearing status on days 1, 7 and 10 ($p>0.05$). In Group B, however, temporary increase in hearing thresholds was observed on day 7, although no differences were found in the statistical analysis.

VDSs at the 24th hour of Group A (Mean ± SD; 5.43±1.3) and Group C (Mean ± SD; 3.57±1.4) were significantly higher compared to Group B (Mean ± SD; 0.00) and Group D (Mean ± SD; 0.57±1.1) ($p<0.05$).

The statistical analysis of the VDSs between Groups A and C showed non-significant differences ($p>0.05$). In both groups, vestibular damage was identified at the maximum level on the 10th day.

In Groups A and C, microscopic damage in the organ of corti, the stria vascularis, the spiral ganglion, the cochlear nerve, the outer hairy cells, the support cells, and the basilar membrane were recorded. Neuronal degeneration and sparsely located neurons were detected in the spiral ganglion. Group C scored the highest in the histological results. However, the pair-wise analysis did not show any significant differences between Group A (Mean ± SD; 13.14±1.2) and Group C (Mean ± SD; 14.29±1.1) ($p>0.05$). To sum up, common and combined cochleovestibular damage was evident in Groups A and C, without a tendency for isolated involvement of either the cochlea or the vestibule.

According to the pair-wise analysis, on the other hand, the total histological damage scores of Group B (Mean ± SD; 2.71±1.7) and Group D (Mean ± SD; 1.71±1.6) were very low and not significantly different from each other ($p>0.05$).

The results of frequency specific ABR thresholds, VDS, and HS of the groups on days 0, 1, 7, and 10, and the intra- and inter-group differences are summarized in Table 3 and shown in Figures 1, 2, and 3.

Table 3. Results of outcome measures of the groups on days 0, 1, 7, and 10; and the significance values of the statistical analyses between groups and measurements

			Day 0	Day 1	Day 7	Day 10	Friedman p
ABR 4 kH	Group A (gentamicin, n=7)	Mean ± SD	22.14±9.1	25.71±3.5	40.71±1.9	51.43±18	**0.00***
		Median (min, max)	20 (10–40)	25 (20–30)	40 (40–45)	40 (40–85)	
	Group B (CLHA, n=7)	Mean ± SD	19.29±3.5	22.14±2.7	32.71±4.6	22.86±2.7	**0.00***
		Median (min, max)	20 (15–25)	20 (20–25)	35 (25–39)	25 (20–25)	
	Group C (gentamicin + CLHA, n=7)	Mean ± SD	22.14±2.7	26.43±2.4	52.86±6.4	40±10	**0.00***
		Median (min, max)	20 (20–25)	25 (25–30)	50 (45–65)	35 (30–60)	
	Group D (saline, n=7)	Mean ± SD	19.29±1.9	20±0	23.57±4.8	20±2.9	0.05
		Median (min, max)	20 (15–20)	20 (20–20)	20 (20–30)	20 (15–25)	
	Kruskal–Wallis p		0.26	0.01	0.00	0.00	
ABR 8 kHz	Group A (gentamicin, n=7)	Mean ± SD	21.43±5.6	30.71±3.5	55.71±16	72.14±20	**0.00***
		Median (min, max)	25 (10–25)	30 (25–35)	60 (35–80)	65 (55–105)	
	Group B (CLHA, n=7)	Mean ± SD	21.43±3.8	26.43±7.5	39.86±8.2	36.43±3.8	**0.00***
		Median (min, max)	20 (15–25)	25(15–40)	39(30–55)	35 (30–40)	
	Group C (gentamicin + CLHA, n=7)	Mean ± SD	22.14±2.7	28.57±5.6	58.57±7.5	51.43±14	**0.00***
		Median (min, max)	20 (20–25)	30 (20–35)	55 (55–75)	45 (35–70)	
	Group D (saline, n=7)	Mean ± SD	17.86±2.7	22.14±3.9	25±4.1	17.86±5.7	**0.02***
		Median (min, max)	20 (15–20)	25 (15–25)	25 (20–30)	15 (15–30)	
	Kruskal–Wallis p		0.10	0.02	0.00	0.00	
ABR 16 kHz	Group A (gentamicin, n=7)	Mean ± SD	12.86±2.7	23.57±4.8	61.43±17	68.57±18	**0.00***
		Median (min, max)	15 (10–15)	20 (20–30)	55 (45–90)	65 (45–95)	
	Group B (CLHA, n=7)	Mean ± SD	14.29±3.5	19.29±3.5	33.57±6.3	30±5.8	**0.00***
		Median (min, max)	15 (10–20)	20 (15–25)	30 (25–40)	30 (25–40)	
	Group C (gentamicin + CLHA, n=7)	Mean ± SD	14.29±1.9	20±0	62.86±9.9	47.14±13	**0.00***
		Median (min, max)	15 (10–15)	20 (20–20)	60 (45–75)	45 (30–65)	
	Group D (saline, n=7)	Mean ± SD	16.43±3.8	15±4.1	19.29±3.5	17.86±5.7	0.38
		Median (min, max)	15 (10–20)	15 (10–20)	20 (15–25)	15 (15–30)	
	Kruskal–Wallis p		0.22	**0.00***	**0.00***	**0.00***	
ABR 20 kHz	Group A (gentamicin, n=7)	Mean ± SD	15.71±1.9	22.14±6.4	62.86±11	69.29±12	**0.00***
		Median (min, max)	15 (15–20)	20 (15–30)	65 (45–75)	65 (55–85)	
	Group B (CLHA, n=7)	Mean ± SD	18.57±2.4	18.57±2.4	37.14±9.5	35±5	**0.00***
		Median (min, max)	20 (15–20)	20 (15–20)	35 (25–55)	35 (30–40)	
	Group C (gentamicin + CLHA, n=7)	Mean ± SD	16.43±2.4	21.43±3.8	61.43±10	61.43±9.9	**0.00***
		Median (min, max)	15 (15–20)	20 (15–25)	65 (45–75)	60 (45–75)	
	Group D (saline, n=7)	Mean ± SD	16.43±3.8	17.14±2.7	20.71±3.5	20±7.6	0.47
		Median (min, max)	15 (10–20)	15 (15–20)	20 (15–25)	15 (15–35)	
	Kruskal–Wallis p		0.22	0.13	**0.00***	**0.00***	
ABR 32 kHz	Group A (gentamicin, n=7)	Mean ± SD	17.86±2.7	28.57±4.8	78.57±7.5	82.86±7	**0.00***
		Median (min, max)	20 (15–20)	25 (25–35)	80 (65–90)	85 (75–95)	
	Group B (CLHA, n=7)	Mean ± SD	21.43±3.8	24.29±4.5	45.71±10	42.86±4.9	**0.00***
		Median (min, max)	20 (15–25)	25 (20–30)	50 (35–55)	45 (35–50)	
	Group C (gentamicin + CLHA, n=7)	Mean ± SD	20±4.1	24.29±3.5	61.43±9.9	61.43±9.9	**0.00***
		Median (min, max)	20 (15–25)	25 (20–30)	60 (45–75)	60 (45–75)	
	Group D (saline, n=7)	Mean ± SD	19.29±1.9	18.57±2.4	25±2.9	22.86±6.4	**0.01***
		Median (min, max)	20 (15–20)	20 (15–20)	25 (20–30)	20 (15–35)	
	Kruskal–Wallis p		0.25	**0.00***	**0.00***	**0.00***	

Table 3. Continued

			Day 0	Day 1	Day 7	Day 10	Friedman p
	Group A (gentamicin, n=7)	Mean ± SD	0±0	5.43±1.3	11.29±1.7	14.86±2.4	**0.00***
		Median (min, max)	0 (0–0)	6 (4–7)	12 (9–13)	16 (11–17)	
	Group B (CLHA, n=7)	Mean ± SD	0±0	0.00	1.57±1	1.43±1.3	**0.00***
		Median (min, max)	0 (0–0)	0 (0–0)	2 (0–3)	1 (0–3)	
	Group C (gentamicin + CLHA, n=7)	Mean ± SD	0±0	3.57±1.4	9.71±1.6	10.71±3.3	**0.00***
		Median (min, max)	0 (0–0)	3 (2–5)	9 (8–13)	9 (9–18)	
	Group D (saline, n=7)	Mean ± SD	0±0	0.57±1.1	0.86±1	1.14±1.5	0.18
		Median (min, max)	0 (0–0)	0 (0–3)	1 (0–2)	1 (0–4)	
	Kruskal–Wallis p		1.00	**0.00***	**0.00***	**0.00***	
HS	Group A (gentamicin, n=7)	Mean ± SD	13.14±1.2		**ANOVA p**	Post-hoc comparison and p	
		Median (min, max)	13 (12–15)			Group A-B	**0.00***
	Group B (CLHA, n=7)	Mean ± SD	2.71±1.7			Group A-C	0.89
		Median (min, max)	3 (1–5)		0.00*	Group B-C	**0.00***
	Group C (gentamicin + CLHA, n=7)	Mean ± SD	14.29±1.1			Group A-D	**0.00***
		Median (min, max)	13 (13–16)			Group C-D	**0.00***
	Group D (saline, n=7)	Mean ± SD	1.71±1.6				
		Median (min, max)	1 (0–5)			Group B-D	1.00

Statistical analysis of audiological, vestibular and histological effects. In this table, there are analyzes showing whether the audiological (ABR: 4, 8, 16, 20, 32 kHz)

ABR: Auditory brainstem response, kHz: KiloHertz, VDS: Vestibular dysfunction score, HS: Histological damage score, CLHA: Cross-linked hyaluronic acid, n: Number of animals, SD: Standard deviation, Min: Minimum, Max: Maximum

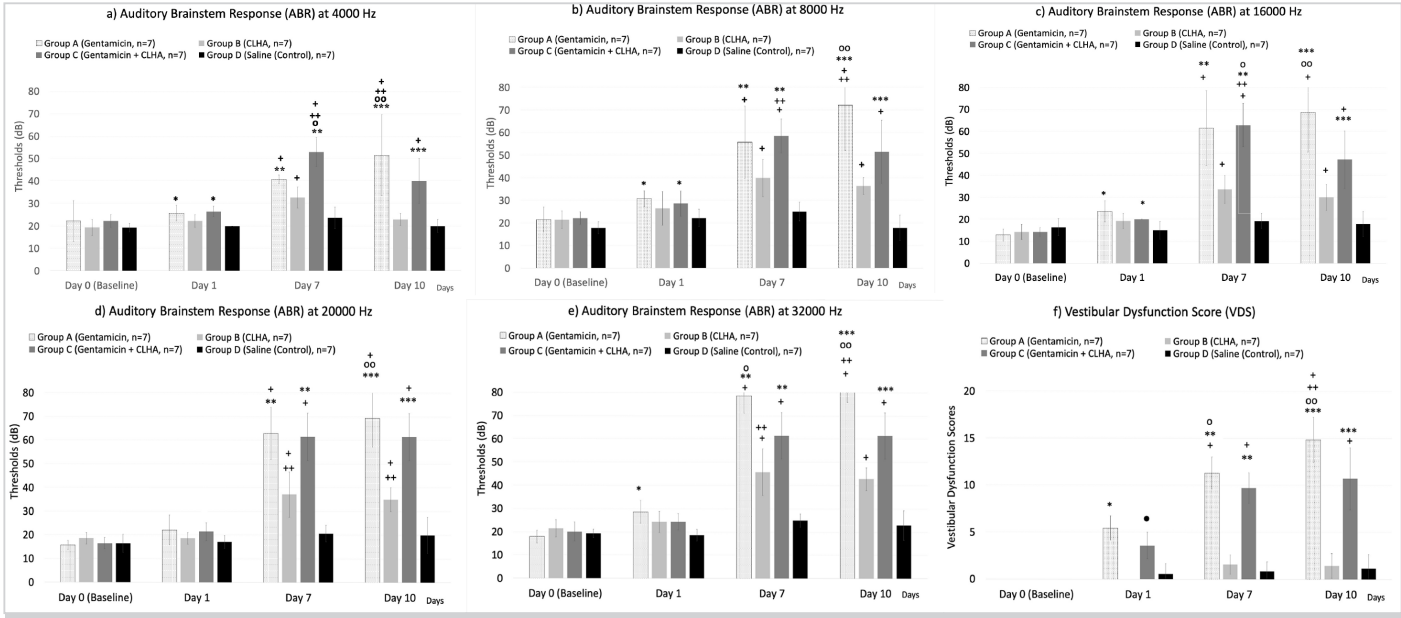

Figure 1. Frequency-specific auditory brainstem responses (ABR) and vestibular dysfunction scores (VDS) of animals (n=28) regarding groups. a) ABR at 4000 Hz, b) ABR at 8000 Hz, c) ABR at 16000 Hz, d) ABR at 20000 Hz, e) ABR at 32000 Hz, f) VDS

Frequency specific ABR and VDS scores on days 0, 1, 7 and 10.

a) ABR at 4000 Hz, b) ABR at 8000 Hz, c) ABR at 16000 Hz, d) ABR at 20000 Hz, e) ABR at 32000 Hz, f) VDS scores

*: Compared to Group saline on day 1, **: Compared to Group saline on day 7, ***: Compared to Group saline on day 10, o: Compared to Group CLHA on day 7, oo: Compared to Group CLHA on day 10, +: Compared to day 0, ++: Compared to day 1, •: Compared to day 0

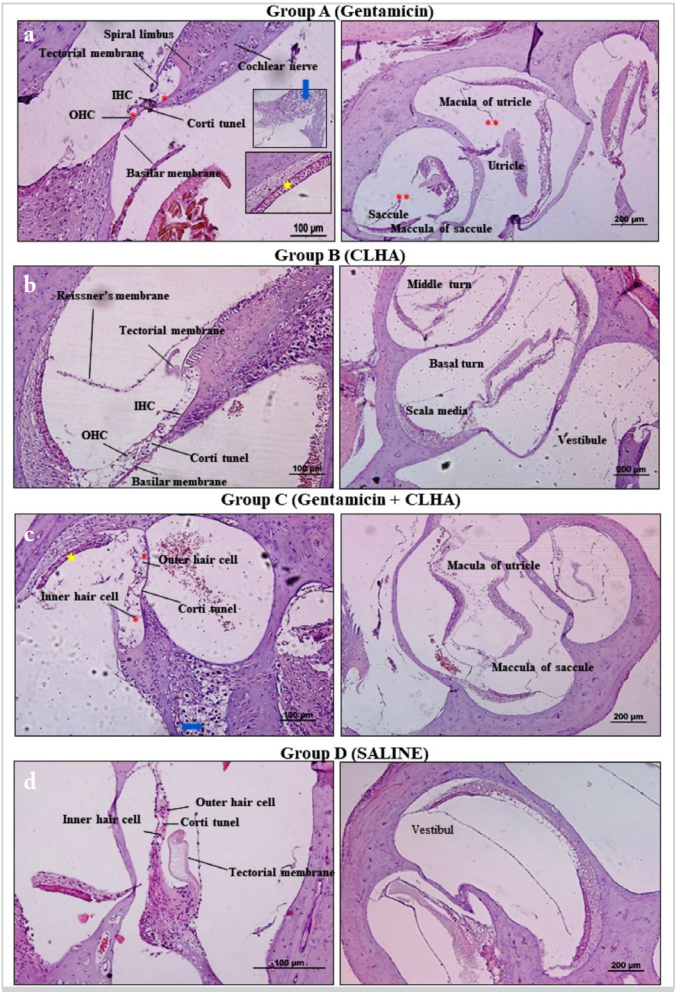

Figure 2. Hematoxylin and eosin stained histological sections. a) Group A (gentamicin) 100 µm–200 µm, b) Group B (CLHA) 100 µm–200 µm, c) Group C (gentamicin + CLHA) 100 µm–200 µm, d) Group D (Saline) 100 µm–200 µm. In Group A, the inner (IHC) and outer hair cell (OHC) loss is very evident (*). The damage in the spiral ganglion, spiral ligament, and basilar membrane, as well as in the utricle and the saccule is significant (**). Intense pycnosis and vacuolization are observed in the stria vascularis (yellow star) and the spiral ligament (blue arrow). Supporting cell loss is evident in the basilar membrane (mm: micrometers). In Group B, the organ of Corti, IHC, OHC, supporting cells and basilar membrane are almost normal. In Group C, cellular vacuolization is observed in cochlear and vestibular sections. The vacuolization and pycnosis in the spiral limbus and the spiral ganglion and the damage in the basilar membrane, supporting cells, OHC and IHC significant. In Group D, the normal histological view of all structures

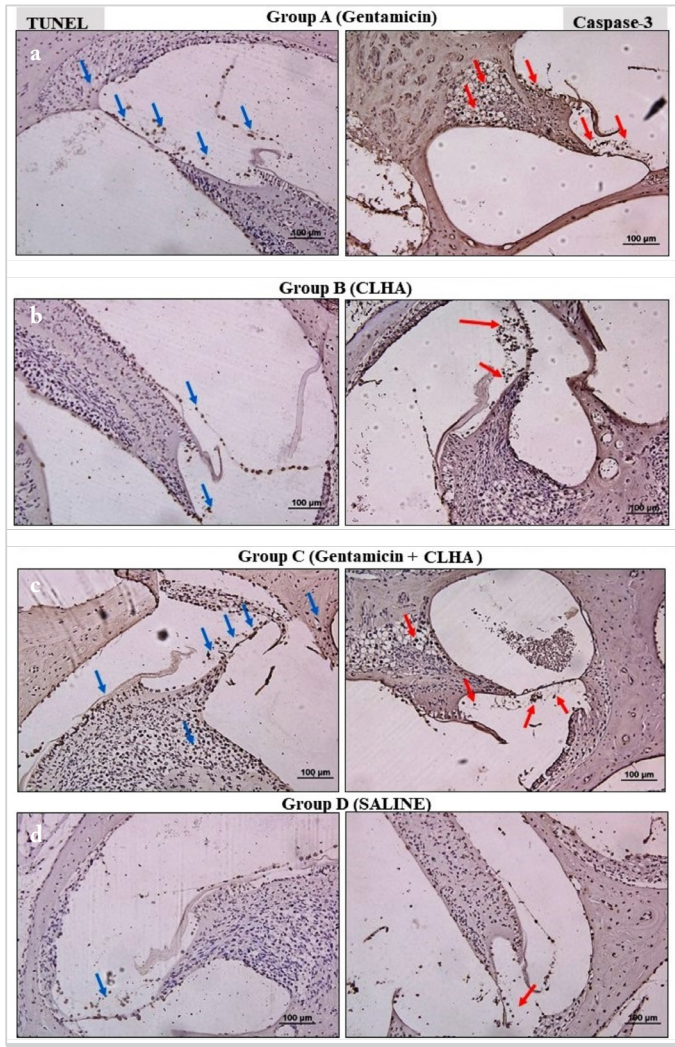

Figure 3. Active caspase-3 and TUNEL histological sections. a) Group A (gentamicin) 100 µm–200 µm, b) Group B (CLHA) 100 µm–200 µm, c) Group C (gentamicin + CLHA) 100 µm–200 µm, d) Group D (saline) 100 µm–200 µm. Representative histochemical TUNEL and caspase-3 immunostaining micrographs (Blue arrows: TUNEL positive cells, Red arrows: Caspase-3 positive cells). In Group A, red arrows indicate areas of TUNEL and activated caspase-3 positive cells. Cells marked by caspase-3, the last step of the apoptotic pathway in active caspase-3 sections, are shown by a red arrow. Mitochondrial stress factor, cytochrome C is visible. In TUNEL sections, deoxyribonucleotide ends exposed after apoptosis turned into a substrate that could not be solved at the endpoints by using terminal deoxyribonucleotide transferase and made visible by reverse methyl staining

Discussion

The transfer pathway of gentamicin from the middle ear to the inner ear remains obscure. Anatomical differences and systemic diseases affect the permeability of the RW and OW (16). According to cadaveric studies, RW and OW blockages were present in 22% and 18% of the population, respectively (17). Another study revealed that RW translucency was not available in 5% of cases and was very low in 13% of cases (18). From the perspective of gentamicin, experimental studies demonstrated that the OW could be dominating its transport (19). However, a more recent study, in contrast to other studies, suggested that most of the gentamicin (57%) intratympanically administered to the ear passed through the RW (1). Furthermore, it has been reported that when intratympanically administered, 66% of gentamicin flowed within the first 24 hours. In contrast, the remaining drug slowly diffused on the following days and were eliminated from the middle ear within 48 hours (20, 21).

Considering this controversy, we aimed to inject a volume that was adequate to completely fill the middle ear.

According to previous studies, when HA is combined with intratympanic drugs, it prolongs drug release, increases the drug's contact with the RW and OW and its diffusion into the inner ear. For instance, combined administration of HA and gentamicin has been reported to extend the release and increase the efficacy of intratympanic gentamicin and boost the perilymph concentration of intratympanic dexamethasone (5, 21). It should also be noted that its molecular structure, such as the presence and ratio of the cross-linked design, plays an essential role in its mode of action (22). It was also observed that gentamicin release kinetics varied according to the dispersion rate in a hybrid material when combined with HA (23).

In our study, gentamicin showed its preliminary cochleo-vestibulotoxic effects in the first 24 hours and continued its action in the following days, in contrast to the results of a study that reported the initiation of cochleotoxicity 5–6 weeks after the application (24). Furthermore, the emergence time of vestibular positive findings was observed to be earlier in our study, in contrast to a previous study which reported that the signs of vestibulotoxicity were observed on the 7th day following gentamicin administration (25).

The literature provides contradictory views regarding the cochleotoxicity of gentamicin. Sheppard et al. (26) stated that there were no findings suggesting that intratympanic gentamicin was vestibular selective. In another study, vestibular toxicity was achieved by intratympanic gentamicin without significant hearing loss; however, histological evidence revealed cellular toxicity in both the cochlea and the vestibule and no statistically significant difference was found between them (27). Güneri et al. (28) reported deterioration in vestibular behavioral tests with combined intratympanic gentamicin and gentamicin-dexamethasone and supported their findings by histological evidence of apoptosis.

The ABR thresholds of Group C worsened similarly to the Group A according to our results, which was also quite different from the previous studies that documented increased risk of hearing loss with sustained gentamicin release from an HA + gentamicin hydrogel compared to gentamicin alone (29). Our audiological findings were also supported by VDS and HS. However, as we used CLHA in our methodology, which is a novel experimental method, we believe that the use of different titrations and administration methods of HA may underlie this discrepancy.

On the other hand, there were no statistically significant differences between Group B and Group D regarding hearing thresholds on days 1, 7, and 10. These results are compatible with previous findings (30). The similarity of the VDS and HS results between these two groups supported the audiological findings as well. However, slight and transient threshold deterioration from day to day was observed at all frequencies in the Group B, which was statistically significant only in intragroup analyses (Table 3). Indeed, this situation was thought to occur due to the cross-linked structure of HA, which caused middle ear effusion (detected by otomicroscopic examinations) as a minor and transient adverse event while enhancing the stabilization of the HA (2, 3, 8).

We agree that, as we did not measure the absorption time, half-life, and middle ear concentration of gentamicin and CLHA in our experimental model, it may not be entirely convenient or reliable to make a clear inference from our results. This should be highlighted as a major limitation of this study. However, as a strength of our study, we utilized caspase-3 and TUNEL assays to reveal accurate histological results since H&E staining may confuse the definitive diagnosis of apoptosis as it only provides information about the morphological changes that may also occur with mechanical trauma (15, 25). Nevertheless, since we did not find any significant differences in audiological, vestibular, and histological parameters between groups A and C, and groups C and D, we assume that CLHA has no long-lasting effects on the cochlea and vestibule, other than causing temporary middle ear effusion.

Conclusion

This study evaluated the cochlear and vestibular effects of intratympanic gentamicin, gentamicin + CLHA, and CLHA alone and compared them with those of the control subjects. We believe that the novel use of gentamicin + CLHA and assessment of cochleo-vestibolotoxicity in all aspects, including both audiological and vestibular test battery, H&E staining, and apoptosis markers make our study a notable contribution to the literature. Despite the previous reports that have focused on the potential impact of HA on drug pharmacokinetics, which may alter the final efficacy or safety of the drug, we did not find any significant and permanent effect of CLHA, whether alone or in combination with gentamicin, on both the cochlea and the vestibule. We plan to elucidate the exact mechanisms underlying our results by further well-designed pharmacodynamic and pharmacokinetic studies.

Ethics Committee Approval: This research was approved by the Dokuz Eylül University Local Ethics Committee (protocol date: 07/18/2018 and protocol number: 52/2018). All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Informed Consent: Experimental animal study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.E., Concept: A.Ç.Ç., S.M.D., G.K., Design: S.Ç.M., O.Y., E.A.G., Data Collection and/or Processing: E.E., S.M.D., S.Ç.M.,

Analysis and/or Interpretation: P.K., Literature Search: E.E., A.Ç.Ç., Writing: E.E., E.A.G.

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

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Main Points

- This is the only study in the literature that monitors cellular changes in both cochlear and vestibular levels and measures behavioral balance tests and audiological tests.
- While hyaluronic acid has been tried many times in other fields for 'prolonged drug release', its combined application with gentamicin in the inner ear is rare.
- Hyaluronic acid production technologies have been increasing in recent years. The combination produced by cross-linking technology hyaluronic acid and gentamicin is also unique in this context.
- Most of the studies in the literature advocate the benefits of hyaluronic acid and its cross-linked versions. However, in our study, neither a long-term drug release effect of hyaluronic acid nor a benefit for regeneration effect in toxicity in the inner ear was observed.

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Bilateral Barotraumatic Involvement of the Infraorbital Nerve with Dehiscence and Ectopic Course: A Case Report

Case Report

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Abstract

The infraorbital nerve is responsible for the sensory innervation of the lower eyelid, the lateral nose, the cheek, the upper lip, and the maxillary teeth. It passes along the infraorbital canal, which runs superior to the maxillary sinus. Dehiscence of the infraorbital canal and its ectopic course in the maxillary sinus is a rare variation. A nerve with these variations may be affected by pathologies in the maxillary sinus and this may constitute a rare cause of facial pain. In this report, we present the clinical symptoms of a 29-year-old male patient who had an infraorbital nerve with an ectopic course and dehiscence in light of the literature.

Keywords: Barotrauma, facial pain, maxillary nerve, nasal decongestants, trigeminal nerve diseases, case report

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Introduction

Facial pain is one of the most common reasons for admission to the otorhinolaryngology outpatient clinics. Among the causes of facial pain, inflammatory pathologies of the nose and paranasal sinuses, dental pathologies, neurological causes such as migraine, ophthalmological disorders, and temporomandibular joint disorders can be listed (1). It is known that most pain in the facial region appears as reflected pain regardless of the pathology (1). Variations in the infraorbital nerve can also cause facial pain in this way. Infraorbital nerve dehiscence and ectopic course were reported to be a cause of facial pain (2-6). In this report, we present the clinical characteristics of the infraorbital nerve with the ectopic course and dehiscence in a patient with facial pain and numbness triggered by airplane travel.

Case Presentation

A 29-year-old male patient presented to our clinic with the complaint of pain and numbness in the cheek area on both sides, more often on the left side, when traveling by plane. He stated that he experienced the pain for the last three years every time he traveled by plane, especially during landing, and that the pain resolved within 1–2 hours after getting off the plane. He had no other complaints such as nasal

congestion, nasal discharge, or postnasal drip. He had no history of chronic disease, medication use, or surgery in the head and neck region. No pathology was detected in the otorhinolaryngological physical examination. The patient was evaluated with maxillofacial computed tomography (CT). In the axial, coronal, and sagittal sections, it was observed that the bilateral infraorbital canal had an ectopic course in the maxillary sinus septum. In addition, dehiscence was observed in the bilateral infraorbital canal, more prominent on the left (Figures 1, 2). The CT images showed no additional pathologies that would explain his complaints. Since the area where the patient's complaints occurred was compatible with the distribution area of the infraorbital nerve, we reckoned that the infraorbital nerve, which showed an ectopic course and had dehiscent areas, was affected by the pressure differences experienced during flight. The patient was prescribed a nasal spray containing oxymetazoline hydrochloride (Iliadin Merck 0.05% Dosage Spray, Santa Farma, İstanbul, Turkey) to use before the flight by spraying

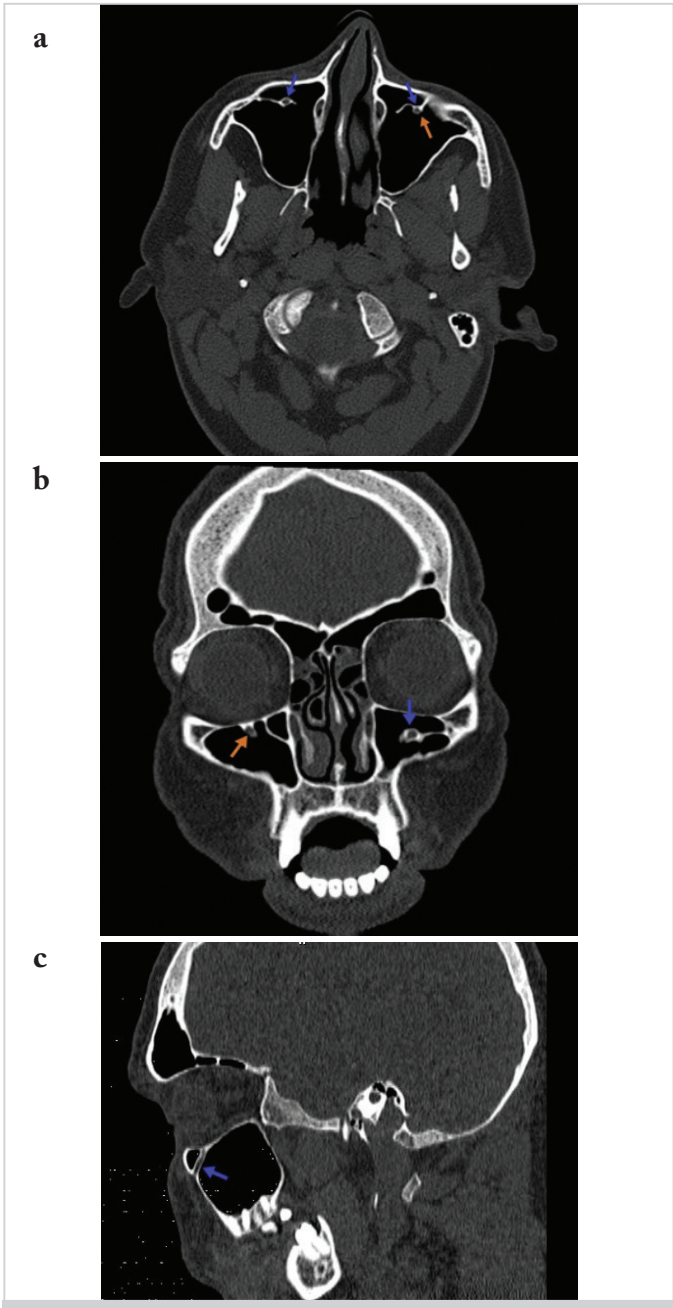

Figure 1. The ectopic course of the infraorbital nerve (blue arrows) and dehiscence areas (orange arrows) prominent on the right side: a) axial section, b) coronal section, c) sagittal section of paranasal sinus computed tomography

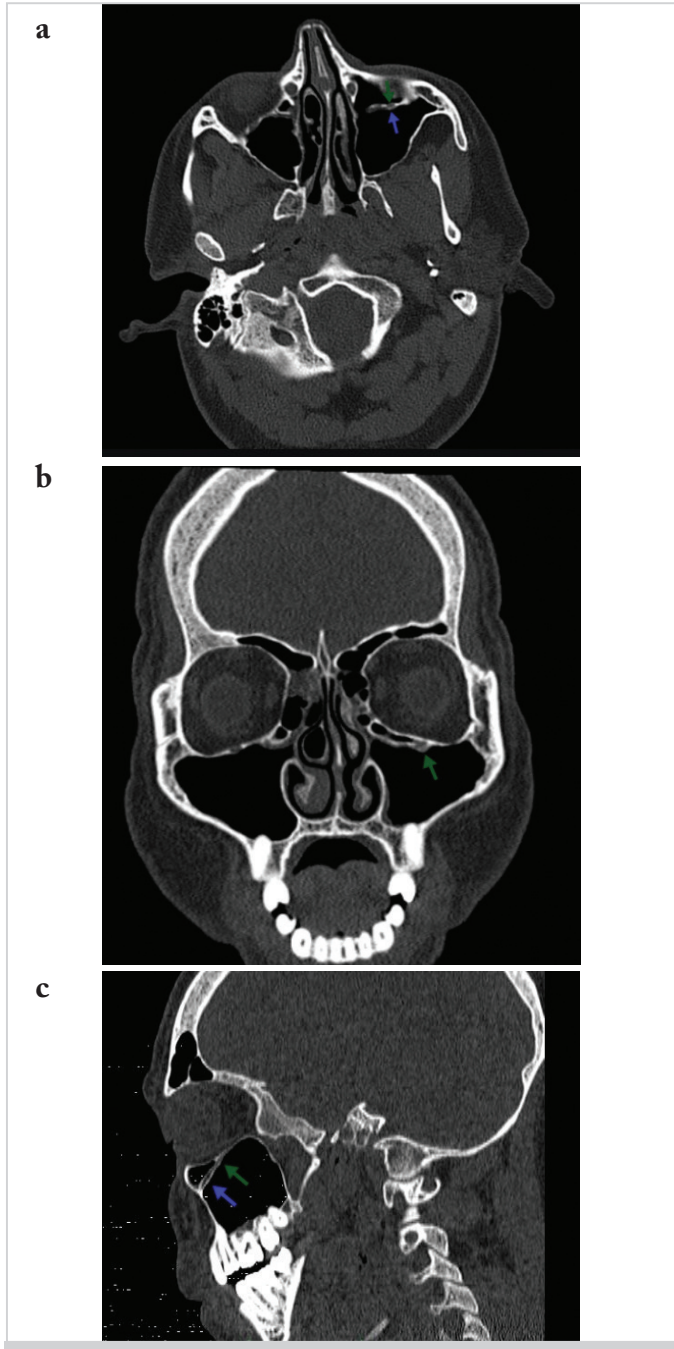

Figure 2. The ectopic course of the infraorbital nerve (blue arrows) and dehiscence areas (green arrows) prominent on the left side: a) axial section, b) coronal section, c) sagittal section of paranasal sinus computed tomography

two times in each nostril. The patient was recommended to return for a follow-up examination two months later. The patient stated that he used the oxymetazoline hydrochloride nasal spray on two flights in two months and his complaints were almost completely gone.

Informed consent was obtained from the patient for this report.

Discussion

The maxillary nerve is part of the trigeminal nerve and its largest cutaneous branch is the infraorbital nerve (5-7). The infraorbital nerve branches from the maxillary nerve in the pterygopalatine fossa and travels through the inferior orbital fissure to enter the orbit. After traveling on the orbit floor, it enters the infraorbital canal (7). The infraorbital canal runs superior to the maxillary sinus, inferior to the orbit, and posterior to anterior (6, 7). The nerve leaves the canal through the infraorbital foramen and provides sensory innervation to the lower eyelid, the lateral nose, the cheek, the upper lip, and the maxillary teeth (4, 6, 7). The sensory innervation of this region may be impaired in maxillofacial fractures, blunt trauma to the cheek, surgery of this region, and rarely due to tumor infiltration (7). In our presented patient, sensory innervation deterioration occurred as pain and numbness in the facial region. That the deterioration in sensory innervation was not due to one of the above-mentioned classical reasons, this case report is remarkable.

The antral wall of the infraorbital canal is thinner than the other walls and has an average thickness of 0.2 mm. The thickness of this wall may vary according to age and the pneumatization of the maxillary sinus (4, 6). Although dehiscence is rare in the antral wall, the rate of dehiscence was reported between 2–16% (2, 6, 8). In a cadaveric study conducted in Thailand, infraorbital canal dehiscence was detected in 15 of 79 cadavers. While seven cases of canal dehiscence were on the right, eight of them were on the left (3). In our case, dehiscence was observed bilaterally. This is not a very common possibility considering cadaveric and radiological studies.

Ectopic course of the infraorbital nerve is a different entity from dehiscence, and ectopic nerve course is also very rare. This rare variation increases the risk of infraorbital nerve injury in sinus surgeries (5). Ference et al. (9) classified the relationship of the infraorbital nerve course with the maxillary sinus into three types: type 1 if the nerve travels completely within the sinus roof, type 2 if the nerve canal is at the inferior edge of the roof and adjacent to the roof, and type 3 if the nerve is inside the lumen and hanging on the septa or the lamella of the infraorbital ethmoid cell. In the same study, the course of the infraorbital nerve of 100 patients (200 nerves) was analyzed and type 1 course was found in 60.5%, type 2 in 27% and type 3 in 12.5%. Our patient had a bilateral type 3 infraorbital nerve course according to this classification. Ectopic course and dehiscence of the infraorbital canal may cause the infraorbital nerve to be affected by pathologies in the sinus (5, 6). Pain from the involvement of the infraorbital nerve is more pronounced in conditions that cause ipsilateral airway obstruction (8). In our patient, there was no pathology such as apparent deviation of the septum or polypoid tissues arising from the ostiomeatal complex, which would cause obstruction in the airway and/or the maxillary sinus. However, there was bilateral facial pain due to barotraumatic nerve involvement. In cases of dehiscence and ectopic course of the infraorbital nerve, well-planned clinical studies are required to prove which etiologic factor causes more pain.

Sharma et al. (4) reported the case of a patient who experienced recurrent pain and paresthesia in the right infraorbital nerve distribution during flight and whose symptoms regressed 30 minutes after landing. In their case, there was a polyp and antral cyst in the middle meatus with ipsilateral infraorbital nerve dehiscence. After surgical treatment, the patient's complaints regressed, and the patient did not experience any symptoms on flights after the treatment. With the presence of dehiscence of the infraorbital nerve, as well as an obstructive nasal pathology, facial pain often benefits from surgical procedures. The patients whose treatment is more challenging are those who do not have obstructive nasal pathology, who do not benefit from medical treatment, and who complain of facial pain. In such cases, infraorbital neuropexy as practiced by Whittet (8) comes to mind as a good option. In this surgical application, the dehiscence is closed artificially by filling the fatty tissue between the mucosa and the nerve.

A study by Chow (1) reported that symptoms occurred during flight and elevator use in a case with stenosis of the maxillary sinus ostium and infraorbital nerve dehiscence. In the article of Whittet and Quiney (2), symptomatic cases were treated surgically by ventilation of the maxillary sinus. McMurray (10) showed that pressure changes occur in the antrum with respiration and these changes decrease as the ostium size increases. It was suggested that the negative pressure effect from stenosis in the paranasal sinus ostia and the subsequent release of local pain mediators such as substance P could cause pain (8). This supports the relief with nasal decongestants in our case. With the use of nasal decongestants, the mucosal edema around the maxillary sinus ostium regresses, thus leading to better ventilation of the maxillary sinus. We believe that a well-ventilated maxillary sinus will better tolerate pressure changes. Surgical treatments applied to the cases in the literature also sought this purpose. In patients who do not respond to nasal decongestants, surgical methods such as uncinectomy may be preferred to increase maxillary sinus ventilation.

Conclusion

Dehiscence and/or ectopic course of the infraorbital canal is rare. We report that dehiscence and/or ectopic infraorbital nerve may cause chronic and recurrent facial pain due to pressure changes. In these cases, we recommend nasal decongestants as a first-line treatment option.

Informed Consent: Informed consent was obtained from the patient for this report.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: V.A., Y.Ç.K., H.Y., V.A.A., E.O., Concept: V.A., Y.Ç.K., H.Y., V.A.A., E.O., Design: V.A., Y.Ç.K., H.Y., V.A.A., E.O., Data Collection and/or Processing: V.A., Y.Ç.K., H.Y., V.A.A., E.O., Analysis and/or Interpretation: V.A., Y.Ç.K., H.Y., V.A.A., E.O., Literature Search: V.A., Y.Ç.K., H.Y., V.A.A., E.O., Writing: V.A., Y.Ç.K., H.Y., V.A.A., E.O.

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

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Main Points

- Dehiscence and/or ectopic course of the infraorbital canal is rare.
- Dehiscence and/or ectopic infraorbital nerve may cause chronic and recurrent facial pain due to pressure changes.
- If no concomitant nasal pathology can be detected in facial pain originating from the infraorbital nerve, nasal decongestants may be the first choice in the treatment.

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Rare Cause of Severe Dyspnea After Tracheotomy-Negative Pressure Pulmonary Edema

Case Report

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Abstract

Deep neck infections are serious conditions and can present with acute upper airway obstruction. Our priority in the treatment is to ensure airway safety, and tracheotomy may be needed to overcome the upper airway obstruction. Unceasing dyspnea after tracheotomy should suggest serious pulmonary pathologies in patients with upper airway obstruction due to deep neck infection. Acute/chronic obstruction resolved after tracheotomy or upper respiratory tract surgical procedures of obstructive sleep apnea patients can turn into severe dyspnea with pulmonary edema. In this report, we present a 46-year-old male patient with negative pressure pulmonary edema as a complication of tracheotomy. The tracheotomy was performed due to severe upper airway obstruction secondary to a deep neck infection. The importance of early diagnosis and prompt treatment of this rare entity after unceasing dyspnea despite tracheotomy is discussed in the light of the current literature

Keywords: Obesity, pulmonary edema, pulmonary gas exchange, sleep apnea syndrome, tracheotomy, case report

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Introduction

In deep neck infections (DNIs), the first priority of treatment is to ensure airway safety, and then it is necessary to review options such as antibiotic therapy and surgical drainage (1). Urgent and/or elective tracheotomy requirement varies between 2.7 and 32.9% in patients experiencing upper airway obstruction after DNIs (1, 2).

Negative pressure pulmonary edema (NPPE) is an important pulmonary complication that is rarely seen after tracheotomy. Upper respiratory tract operations, obesity, short neck, and obstructive sleep apnea syndrome (OSAS) are reported among the factors that increase the risk of developing NPPE (3, 4).

Ensuring airway safety is the first priority in DNI patients and tracheotomy is one of the treatment options (5). In this case report, we present a case of NPPE, a rare postoperative complication that could be mortal if misled. Written and verbal consent was obtained from the patient for this report.

Case Presentation

A 46-year-old male patient presented to our clinic with worsening tonsillopharyngitis while on antibiotics

for five days. Physical examination and computed tomography (CT) revealed multiple abscess foci in the deep neck spaces and severe trismus (Figures 1, 2). Preoperative thoracic CT imaging was within normal limits. The patient had diabetes mellitus, OSAS (with the use of continuous positive airway pressure device), heart rhythm disorder, and obesity (body mass index: 37). The patient was taken to the operating room for abscess drainage and tracheotomy. The preoperative risk was stated by the anesthesiologists as American Society of Anesthesiologist 3E. The anesthesiologist predicted the need for an intensive care unit for probable postoperative pulmonary complications due to chronic airway obstruction with OSAS and additional acute respiratory distress with upper airway edema.

Since the patient had trismus, the preoperative examination was performed together with the anesthesiologist, and it was thought that sudden collapse might occur after the administration of muscle relaxants. Therefore, upon the recommendation of the anesthesiologist, the patient was not intubated but a tracheotomy was performed with local anesthesia.

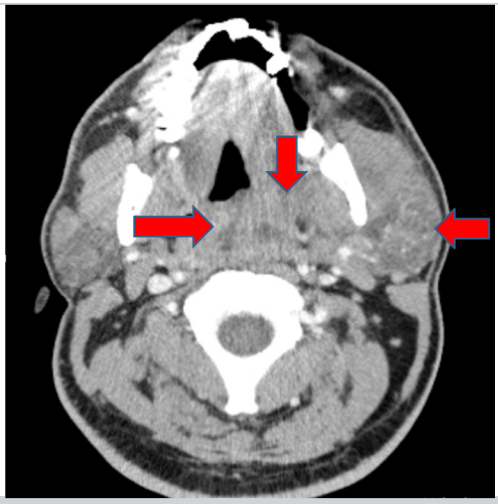

Figure 1. Neck CT image showing peritonsillar-parapharyngeal-intraparotidal multifocal abscess areas (arrows)
CT: Computed tomography

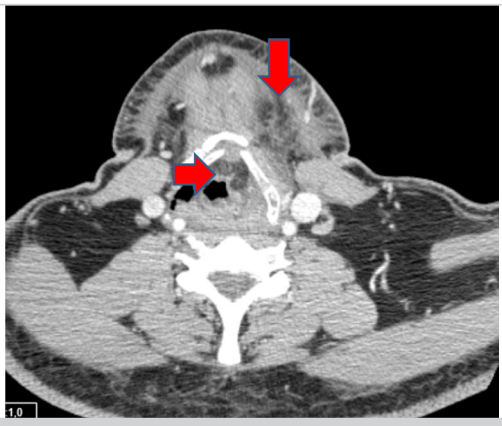

Figure 2. Neck CT, axial section showing abscess foci extending to the larynx (arrows)
CT: Computed tomography

The general anesthesia procedure was then initiated by ventilation through the tracheotomy tube. Emergency tracheotomy and multiple (peritonsillar, parapharyngeal, submandibular, intraparotidal, and intraoral retropharyngeal) abscess drainage were performed, and pathology and abscess culture samples were taken under general anesthesia. Although the patient had an uncomplicated tracheotomy, he had severe dyspnea and low oxygen saturation (80%) after arising from general anesthesia. He was taken to the intensive care unit with the recommendation of the anesthesiologist. Sputum containing very dense foam was aspirated from the tracheotomy cannula and oxygen support of 10 lt/min was administered through the tracheostomy cannula. Thoracic CT imaging revealed predominantly centrally located multifocal ground glass areas and interlobular septal thickenings in both lung parenchyma without mediastinitis findings (Figure 3). Coronavirus disease-2019 was ruled out and differential diagnoses of alveolar hemorrhage and NPPE were considered.

As the patient did not benefit from the oxygen administered via the cannula, decision was made to apply invasive mechanical ventilator (IMV) through the tracheostomy cannula, furosemide infusion for diuresis, and empirical meropenem treatment were started. A control CT was taken 48 hours after the patient's oxygen saturation reached 90%, and it was determined that the abscess foci in the parapharyngeal space of the neck continued and the ground glass appearance of the lung regressed but did not completely disappear. The patient was once more taken to the operating room for abscess drainage. Postoperatively, he was connected to an IMV with the recommendation of the pulmonology department. After three days of IMV, the patient's oxygen saturation improved and his pulmonary symptoms regressed.

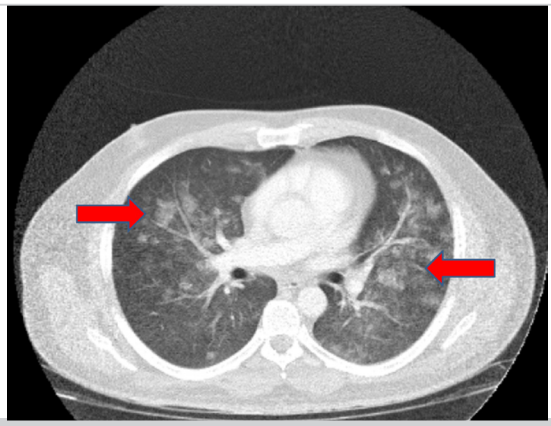

Figure 3. NPPE thoracic CT axial image (arrows)
NPPE: Negative pressure pulmonary edema, CT: Computed tomography

Abscess drainage was performed for the third time 10 days after the second surgery when the patient was suspected of collection in the retropharyngeal area due to fluctuating C-reactive protein and neutrophil levels. The patient was discharged after 30 days with a decannulated tracheotomy after his laryngeal edema regressed and pulmonary problems were completely relieved. No problems were observed in the follow-up visits.

Discussion

The main mechanism of NPPE is that acute closure of the airway causes negative intrathoracic pressure increase caused by forced inspiration against the upper airway, increased pulmonary capillary hydrostatic pressure, and hydrostatic pulmonary edema. Two distinct clinical mechanisms can be identified for NPPE. Type I NPPE occurs soon after the onset of the acute upper airway obstructive process. Type II NPPE develops after the resolution of chronic upper airway obstruction. Most cases of NPPE described in the literature are type I NPPE that develop after the onset of an acute episode of upper airway obstruction. It relies on a different mechanism and process in type II NPPE. Relief of chronic airway obstruction caused by various conditions such as adenotonsillar hypertrophy, laryngotracheal neoplasm, and thyroid goiter can result in type II NPPE (6, 7).

In the presence of forced inspiration, negative pleural pressure can rise well above the normal value. The result is increased venous return to the right heart and dilation of the right ventricle. The interventricular septum shifts to the left, and cardiac output decreases as a result of diastolic dysfunction. Fluid accumulation in the alveoli and pulmonary edema are observed as a result of impaired microvascular circulation and increased pulmonary capillary permeability (8). This often occurs immediately after upper airway obstruction, but symptoms can take up to six hours to appear (3). Pulmonary infiltrates and interstitial pulmonary edema can be seen on chest X-ray or CT. The presence of clinical and radiological findings suggestive of pulmonary edema and the absence of cardiac pathology should suggest the diagnosis of NPPE.

Aspiration pneumonia, cardiogenic pulmonary edema, and mediastinitis are important in its differential diagnosis (9). Type II NPPE is based on a mechanism of chronic upper airway obstruction. Relief of chronic upper airway obstruction caused by various conditions such as adenotonsillar hypertrophy can result in type II NPPE (7). For OSAS patients, respiratory track surgical procedures can also result in pulmonary edema in a similar manner. Our patient had risk factors such as obesity, short neck, upper airway obstruction, tracheotomy, and OSAS. Foamy sputum, low oxygen saturation, severe acute dyspnea, acute severe pulmonary infiltrates, and edema on CT enabled us to make the diagnosis. One of the most common pulmonary pathologies that cause dyspnea in DNI patients is mediastinitis. However, the differential diagnosis was made with thoracic CT in our patient, and mediastinitis was ruled out. The main goal in the treatment of NPPE is to ensure airway patency and adequate oxygenation. Oxygen saturation should be maintained above 90%. In mild cases, an oxygen mask was found sufficient. However, if the patient's clinical and oxygen values do not improve, noninvasive mechanical ventilation (continuous positive airway pressure or bilevel positive airway pressure) should be applied (9). Restriction of intravenous crystalloids, maintenance of normal intravascular volume and serum oncotic pressure with colloids, and use of diuretics may be recommended in the treatment of NPPE. Some authorities recommend steroids in the NPPE treatment regimen. However, the use of steroids for treatment still seems controversial (7).

Conclusion

NPPE can develop in DNI cases after upper airway obstruction or after tracheotomy for the treatment of upper airway obstruction. We share this rare complication of tracheotomy to contribute to the literature.

Informed Consent: Written and verbal consent was obtained from the patient for this report.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.K.B., O.B., C.G.C.E., H.G., O.İ., E.S.Ö., Concept: K.K.B., O.B., C.G.C.E., H.G., O.İ., E.S.Ö., Design: K.K.B., O.B., C.G.C.E., H.G., O.İ., E.S.Ö., Data Collection and/or Processing: K.K.B., O.B., C.G.C.E., H.G., O.İ., E.S.Ö., Analysis and/or Interpretation: K.K.B., O.B., C.G.C.E., H.G., O.İ., E.S.Ö., Literature Search: K.K.B., O.B., C.G.C.E., H.G., O.İ., E.S.Ö., Writing: K.K.B., O.B., C.G.C.E., H.G., O.İ., E.S.Ö.

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Main Points

- Deep neck infections may present with severe upper airway obstruction.
- The primary priority of management is to secure the airway.
- Sudden removal of airway obstruction in patients with risk factors can cause negative pressure pulmonary edema.
- Negative pressure pulmonary edema is a mortal condition and should be treated quickly with a multidisciplinary approach.

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Bilateral Congenital Agenesis of Stapes and Oval Window in Two Members of a Family (Brother and Sister)

Case Report

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Abstract

Congenital agenesis of the stapes and the oval window is rare. Congenital stapedial agenesis (CSA) may be recognized preoperatively in the presence of conductive hearing loss. The principal radiological imaging approach of the temporal bone, computed tomography (CT), can be used to diagnose CSA. Our 17-year-old male patient (case A) had long-term hearing loss which was getting worse. A temporal bone CT scan revealed the absence of the stapes and the oval window on both sides and an abnormal position of the facial nerve. No anomalies were detected in the external ear structures. Explorative right ear tympanotomy revealed an abnormal inferior course and dehiscence of the facial nerve. The oval window and stapedial structures were absent. Patients were evaluated for continued hearing aid use or bone-anchored hearing aid implantation. Similar CT imaging and clinical abnormalities were seen in his 16-year-old sister (case B). They did not have any other siblings and neither of their parents nor any of their relatives had hearing loss. This report presents the CT scans of the two siblings with mixed hearing loss (mainly conductive) and the perioperative image of the first case. A genetic study may help explain the etiopathogenesis since both cases had similar clinical and imaging findings.

Keywords: Hearing loss, congenital anomaly, stapes, oval window, siblings, case report

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Introduction

Congenital absence of the stapes (CSA) together with the oval window is a very rare clinical entity. CSA can be recognized preoperatively in patients with isolated conductive hearing loss (CHL). Computed tomography (CT) is the main imaging method for temporal bone diagnosis. Understanding the anatomy and the embryological origins of the malformation is essential for accurate diagnosis and treatment. CSA may be associated with head and neck anomalies or syndromes (1).

The treatment options for CSA include the use of an air conduction hearing aid, or an implantable bone conductive hearing aid, or surgery. Surgical approaches are explorative tympanotomy with facial nerve rerouting, vestibulotomy, and ossicular reconstruction, or fenestration of the horizontal semicircular canal (2).

Case Presentation

In this report, we present the cases of two siblings with long-term and progressive hearing loss. Case A was a 17-year-old boy and case B was a 16-year-old girl. Their mother had no history of infection, disease, trauma, or drug use during pregnancy. The siblings had no history of disease, otitis media, tinnitus, trauma, or vestibular dysfunction. No pathologies were found on examination. Audiological tests of case A showed bilateral moderate-to-severe mixed hearing loss with a component of bilateral mild sensorineural hearing loss at low frequencies (Figure 1, discrimination 76%). The tests of case B showed bilateral moderate to severe mixed hearing loss with a component of bilateral slight sensorineural hearing loss (Figure 2, discrimination 80%). The mean (0.5 kHz, 1 kHz, 2 kHz, and 4 kHz) air-bone gaps were 36 dB in case A and 45 dB in case B. Weber's tests were in the middle and Rinne's tests were negative bilaterally. Ipsilateral and contralateral acoustic reflexes were negative. There was no nystagmus. Non-contrast axial and coronal plane CT scan (1-mm slice thickness) of the temporal bone revealed no stapes in the tympanic cavities and closed oval windows (Figures 3, 4). The tympanic segment of the facial nerve showed inferomedial course in both of the cases. There were no pathological findings in other ear structures or the mastoid cavity. In case A, exploratory tympanotomy verified the absence of the oval window and the stapes, dehiscence of the tympanic segment of the facial nerve, and the abnormal inferiomedial position of the facial nerve where the oval window should be on the lateral surface of the otic capsule (Figure 5). The malleus and the incus were mobile and intact. Genetic analysis was planned to determine the etiopathogenesis of the patients who had no comorbidities or clinical symptoms.

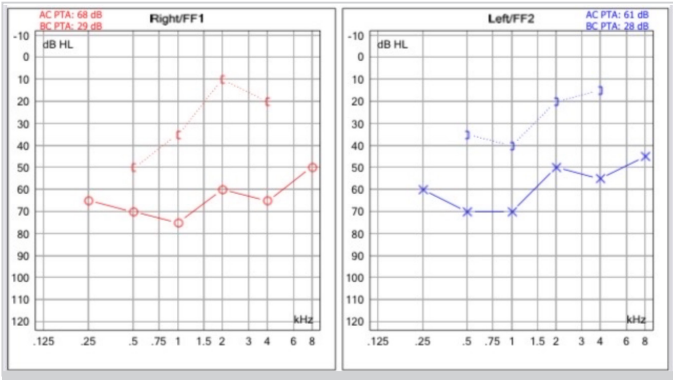

Figure 1. Audiological test of case A: bilateral moderate-to-severe mixed hearing loss with a component of bilateral mild sensorineural hearing loss at low frequencies

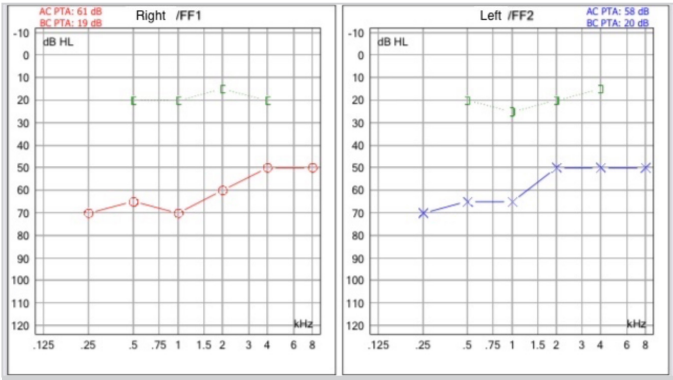

Figure 2. Audiological test of case B: bilateral moderate-to-severe mixed hearing loss with a component of bilateral slight sensorineural hearing loss

Written informed consent was obtained from the patients and the parents.

Discussion

CSA was first described by McAskile and Sullivan in 1955 (2). It is a rare entity of unknown etiology, with stapes and oval window agenesis linked to the abnormal development and course of facial nerve (1-4). A high-resolution temporal CT scan is recommended in cases suspected of congenital middle ear malformations (3). A CT scan can detect the

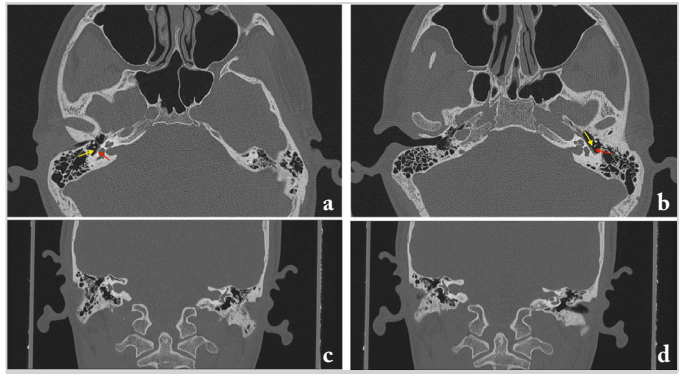

Figure 3. Case A: Right (a–c) and left (b–d) axial and coronal CT scans of the temporal bone showing the bilateral agenesis of the stapes (yellow arrow), the absence of the oval window, and the abnormal position of the facial nerve (red arrow); other ear structures appear normal

CT: Computed tomography

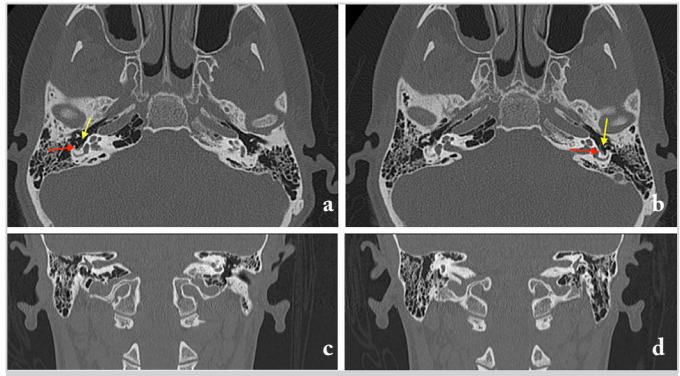

Figure 4. Case B: Right (a–c) and left (b–d) axial and coronal CT scans of the temporal bone showing the bilateral agenesis of the stapes (yellow arrow), the absence of the oval window, and the abnormal position of the facial nerve (red arrow); other ear structures appear normal

CT: Computed tomography

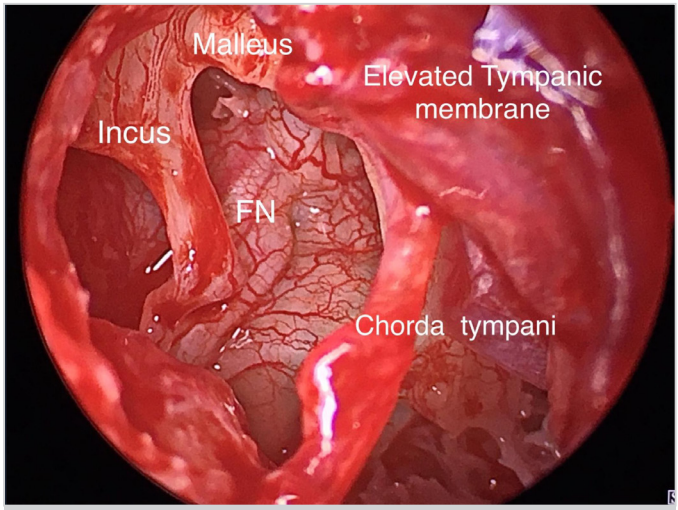

Figure 5. Exploratory tympanotomy image of case A verified the absence of the oval window and the stapes, the dehiscence of the tympanic segment of the facial nerve, and the abnormal inferomedial position where the oval window should be on the lateral surface of the otic capsule. The malleus and the incus are intact and mobile

FN: facial nerve

isolated absence of stapes, or stapes agenesis with oval window aplasia and abnormally located facial nerve in young patients with CHL (3). The stapes, the manubrium of the malleus, and the long process of the incus develop from the second branchial arch or Reichert's cartilage. The horizontal and vertical parts of the facial nerve become recognizable as the stapes develops toward the otic capsule at five to six weeks of pregnancy (1, 2). The stapes invaginates the otic capsule at seven weeks, determining the location of the future window. The tympanic part of the stapes footplate originates from Reichert's cartilage and the vestibular part from the otic capsule (5). If the facial nerve is displaced anteriorly, it prevents contact between the otic capsule and the stapes blastema. Contact is essential for stapes development (1, 2). Differences in this process could explain the observed variations (5). Delayed development of the first branchial arch can lead to the displacement of the facial nerve, and the development of the facial nerve strongly impacts the development of the stapes (1). However, the role of genetic abnormalities in etiopathogenesis is unknown.

CHL in the absence of a trauma, illness, or chronic medication use should be assessed for congenital middle ear abnormalities. Studies in the literature report that congenital hearing loss is usually more severe than in acquired cases (2, 3).

The typical CSA audiograms are flat, pure tone at speech frequencies, but not pathognomonic. It may not always be present, as in our cases (2). Interestingly, the observation of mixed hearing loss due to mild sensorineural hearing loss at low frequencies without dizziness in Case A could be due to a genetic etiopathogenesis such as enlarged vestibular aqueduct syndrome causing progressive sensorineural hearing loss (6).

Treatment in CSA is controversial due to a lack of publications (1). Treatment options include vestibulotomy, ossicular reconstruction, fenestration of the horizontal semicircular canal, and hearing aids (2). If possible, ossicular chain reconstruction is preferred. Displacement of the facial nerve between the remaining ossicles and the oval window is a problem. Because of the potential danger of abnormal course of the facial nerve, preoperative CT scanning is recommended to detect congenital CHL (1).

After the cases reported by Yi et al. (7), our cases are the second two siblings with bilateral CSA and oval window agenesis in the literature. The abnormally located facial nerve and the high risk of nerve damage due to the malformation seen in our cases suggested that the implantation of a hearing aid or bone anchored hearing aid (BAHA) instead of reconstruction would provide better functional results. It was decided to continue with the treatment with hearing aids, as the patients did not prefer BAHA for aesthetic reasons.

In conclusion, a collaboration between radiologists and clinicians in CSA cases contributes significantly to the diagnosis and planning of appropriate treatment, which should be individualized. A family history of CSA cases with mixed hearing loss suggests the necessity of genetic analysis.

Informed Consent: Written informed consent was obtained from the patients and the parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

Conflict of Interest: There is no conflict of interest to disclose.

Financial Disclosure: The authors declared that this study has received no financial support.

Main Points

- Our cases are the second two siblings in the literature with bilateral congenital stapedial agenesis and oval window agenesis.
- In the diagnosis of such cases, it is important to recognize the presence of an abnormally located facial nerve due to the high risk of nerve damage in the operation related to the malformation.
- The familial history suggests that genetic basis should be investigated.

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