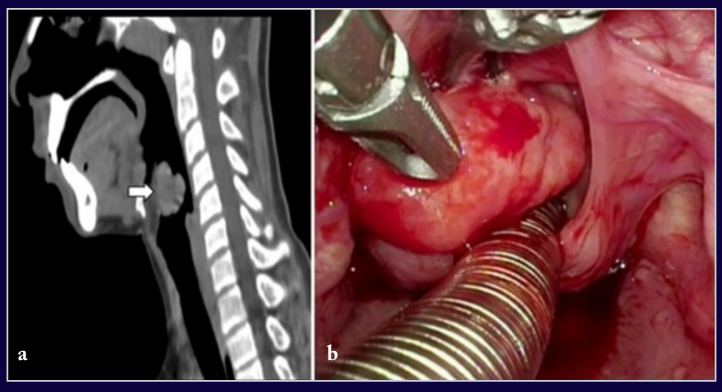
Indexed in PubMed and Web of Science

E-ISSN 2667-7474

Volume 61 ~ Issue 2 ~ June 2023

Turkish Archives of Otorhinolaryngology

Official Journal of the
Turkish Otorhinolaryngology
Head and Neck Surgery Society



Recurrent Pediatric Extranasopharyngeal Angiofibroma of the Epiglottis: Case Report

Original Investigations

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Türk Otorinolarengoloji Arşivi

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Web: www.galenos.com.tr **Publisher Certificate Number:** 14521

Publication Date: September 2023
E-ISSN: 2667-7474

International scientific journal published quarterly.

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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readers and experts concerning the published studies, articles about general practice and subject of the journal with historical content, memories of scientific significance, educative and catechetical manuscripts about medical deontology and publication ethics.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

E-ISSN: 2667-7474

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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
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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.

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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.

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.

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

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.

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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.

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach

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Video Article	N/A	1500	250 (Structured)	106	2	2
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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

SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the complete drug reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92.

Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki öğrencilerin beslenme durumları, fiziksel aktiviteleri ve beden kitle indeksleri kan lipidleri arasındaki ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

E-pub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: https://www.cdc.gov/ncidodlElD/cid.html.

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Contents

What Is the Role of Sensorineural Hearing Loss in Fabry Disease Screening?

Original Investigation

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Abstract

Objective: Fabry disease is a rare hereditary lysosomal storage disease caused by the deficiency of alpha-galactosidase A (α-GLA). Although sensorineural hearing loss is common in Fabry disease, there are no studies in the literature that have screened a population with sensorineural hearing loss for Fabry disease. In this study, we aimed to screen a group of patients who were diagnosed with sensorineural hearing loss and underwent a hearing test for Fabry disease.

Methods: One hundred sixty eight patients who were aged 18–75 years and diagnosed with idiopathic hearing loss between July 2019 and January 2020 were included. In male patients, α-GLA enzyme activity was analyzed. Patients with low enzyme activity were identified and genetic testing was performed for mutations in the *GLA* gene. In females, only genetic testing was performed.

Results: Eighty four women and 84 men were included in the study. α-GLA enzyme activity was low in 11 of the 84 male patients (13%). One out of these 11 patients had a gene mutation for Fabry disease. Moreover, four relatives of this index patient were diagnosed with Fabry disease in family screening. GLA gene mutation was also found in one of the 84 female patients. Consequently, two (1.2%) of our 168 patients were diagnosed with Fabry disease by screening with enzyme activity and genetic testing.

Conclusion: Our study showed that screening for Fabry disease in patients with idiopathic sensorineural hearing loss without other specific findings might be a useful strategy for detecting new cases.

Keywords: Fabry disease, sensorineural hearing loss, lysosomal storage diseases, genetic testing, alpha-galactosidase

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Cite this article as: *Köroğlu EY, Gökçay Canpolat A, Yılmaz S, Demir Ö. What Is the Role of Sensorineural Hearing Loss in Fabry Disease Screening?. Turk Arch Otorhinolaryngol 2023; 61(2): 52-57*

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Received Date: 10.04.2023
Accepted Date: 04.08.2023

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DOI: 10.4274/tao.2023.2023-3-10

Introduction

Fabry disease is a lysosomal storage disease caused by the deficiency of alpha-galactosidase A (α-GLA) and shows X-linked transition (1). The findings usually begin to present in childhood. If untreated, often life-threatening complications develop when individuals reach their middle age (2). The incidence of Fabry disease is between 1:40,000 and 1:117,000 worldwide (3). However, since the findings of Fabry disease are non-specific, it is thought that some of the cases cannot be detected during the individuals' lifetime (1). Currently, neonatal screening programs for Fabry disease are being carried out in some countries, and there is a higher prevalence between 1:1,368 and 1:8,882

in these countries (4-7). These findings reveal that Fabry disease is more common than previously reported (8). That the disease has an X-linked transition and consanguineous marriages are frequent in Turkey suggests that Fabry disease can be more commonly detected in closed communities in which kinship marriages are common.

As well as many complications such as cardiomyopathy, hypertension, arrhythmia, proteinuria, renal failure, and stroke, Fabry disease causes hearing-related conditions. Tinnitus is usually the first auditory symptom and presents in approximately 27–38% of the patients (9). Many patients develop progressive sensorineural hearing loss, especially in adulthood. In a study of 68 Fabry disease patients, sensorineural hearing loss was detected in 58.8%, in whom the severity of sensorineural hearing loss and the severity of renal and cardiac functions were parallel. In these patients, hearing loss was observed as asymmetrical, starting unilaterally and then affecting the contralateral side (10).

Studies have been conducted on the incidence of Fabry disease in patients who had idiopathic clinical findings (end-stage renal failure, hypertrophic cardiomyopathy, stroke) (11-16). As a result of these studies, the incidence of Fabry disease was found to be more common in this group of patients than in the general population, hence it was concluded that screening for Fabry disease would be beneficial in similar clinical cases.

In our study, Fabry disease was screened in patients with idiopathic sensorineural hearing loss. It aimed to create a new screening strategy for this disease in which complications can be prevented with early treatment after diagnosis.

Methods

Patients who underwent audiometry as part of the routine practice at the otorhinolaryngology department between July 2019 and January 2020, and were found to have sensorineural hearing loss without a known etiology in otorhinolaryngologic examination were included in the study. Patients younger than 18 years, patients with known Fabry disease, and patients whose cause of sensorineural hearing loss could be explained by any other factor (trauma, drug use, infection, systemic diseases) were excluded. An a priori power analysis was done to determine the number of patients in the study.

An Otometrics Madsen Astera 2 (Natus Medical, Taastrup, Denmark) device was used for pure tone audiometry. World Health Organization's grades of hearing impairment were used for the classification of hearing loss (17).

In female patients, first Fabry gene mutation was studied, and in male patients, α-GLA enzyme activity was studied first by taking dry blood samples. The presence of Fabry gene mutation was also investigated later in male patients who had low enzyme activity (<2.50 nmol/mL/hours). The reason for examining genetic mutations without measuring the enzyme level in women is that this disorder is caused by mutations in the gene located on the X chromosome. Because of its X-linked inheritance pattern, males with a single copy of the mutated gene typically exhibit symptoms of the disease, while females (who have two X chromosomes) might be carriers or, in some cases, exhibit milder symptoms due to the presence of a normal copy of the gene on the other X chromosome (1). Family screening was also done for the patients diagnosed with Fabry disease. Samples required for measuring α-GLA enzyme activity and determining GLA gene mutation were prepared by 5 milliliters of blood samples taken from the patients and dropping them onto dry blood filter paper simultaneously The dry blood sample filter papers were delivered to the laboratory on the same day where they were examined by fluorimetric methods. The National Center for Biotechnology Information Genomic reference sequence: NG_007119.1, NM_000169.2 was used as the reference sequence for GLA gene mutations.

As a result of the tests, patients whose hearing loss etiology had been linked only to Fabry disease were proportioned to the total study population.

Electrocardiography, echocardiography, spot urine protein/creatinine ratio, and eye and skin examinations were done to detect other organ involvements in patients diagnosed with Fabry disease.

The study was approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (decision no: I1-08-19, date: 25.06.2019) and conducted in line with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Statistical Analysis

Statistical analyses were done using IBM SPSS Statistics for Windows (IBM Corp, Version 22.0). The Kolmogorov–Smirnov test was used to assess the normality of continuous data. Categorical variables were presented as numbers and percentages (%). Continuous data were displayed as mean ± standard deviation for normally distributed variables and median (minimum-maximum) for non-normally distributed variables. The chi-square test was used to compare the percentages of hearing loss and the severity levels between genders.

Results

Of the total 168 patients included in the study, 84 were female and 84 were male. Patient characteristics are summarized in Table 1.

α-GLA activity was found below 2.50 nmol/mL/hour in 11 (8.4%) of the 84 male patients. When the Fabry gene

Table 1. Patients' ages and sensorineural hearing loss characteristics

	Women (n=84)	Male (n=84)	Total (n=168)
Age	56.3±12.6	55.0±14.0	55.6±13.3
The beginning of the hearing loss			
Sudden	11 (13%)	16 (19%)	27 (16%)
Quiet	73 (87%)	68 (81%)	141 (84%)
Hearing loss involvement			
Bilateral	64 (76%)	74 (88%)	138 (82%)
Unilateral	20 (24%)	10 (12%)	30 (18%)
Hearing loss severity			
Mild	36 (43%)	36 (43%)	72 (43%)
Moderate	30 (36%)	31 (37%)	61 (37%)
Severe	18 (21%)	17 (20%)	35 (20%)
Tinnitus	39 (46%)	46 (54%)	85 (50%)

mutation was studied in these patients, only one patient (Index case 1) had a mutation that was proven to cause Fabry disease. The mutation detected in this patient was stated as c.1010T> C(p.F337S) hemizygote.

One out of the 84 female patients had one of the mutations proven to cause Fabry disease. The mutation detected in this patient (Index case-2) was identified as c.937G> T(p. D313Y) heterozygous. As a result, Fabry disease was found in two (1.2%) (2/168) of all patients included in the study.

The study design and the results obtained are given in Figure 1.

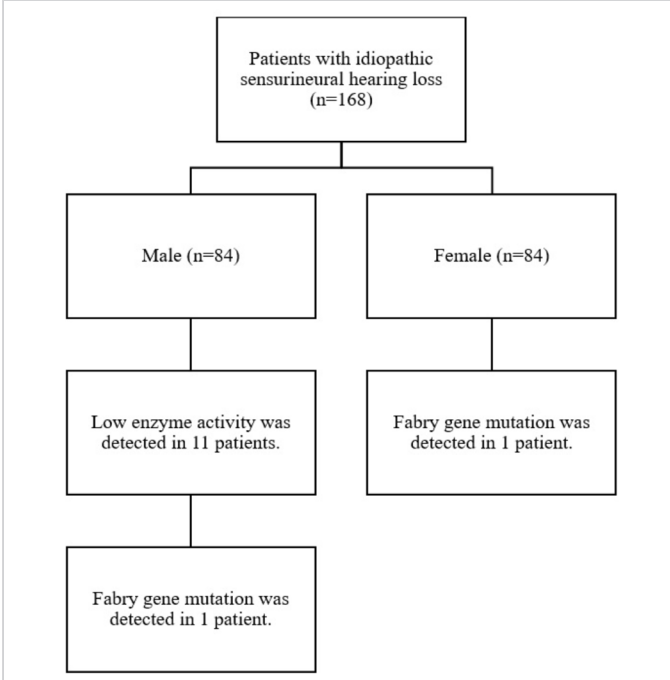

Figure 1. Study design and results obtained

Index Case-1

The only male patient with a gene mutation associated with Fabry disease was 61 years old. The patient was on follow-up for chronic kidney disease since he was in his 30s. The etiological cause of the patient's chronic kidney failure could not be determined in that period and was accepted as idiopathic. The patient was started on hemodialysis in 2009. The patient's proteinuria level could not be determined due to his anuric state.

In the previous and present echocardiograms of the patient who described intermittent effort dyspnea during the follow-up period for chronic renal failure, progressive myocardial hypertrophy was found, although the ejection fractions were in the range of 40–45%. The patient whose myocardial hypertrophy etiology could not be found was diagnosed with idiopathic hypertrophic subaortic stenosis. The patient was diagnosed with atrial fibrillation a few years after the beginning of hemodialysis treatment. With complaints of dizziness after a routine hemodialysis session in December 2018, a full atrioventricular block was detected and a permanent pacemaker was placed. The patient's ejection fraction was 45% in his echocardiography taken at that time, and the septum was extremely hypertrophic.

After the diagnosis of Fabry disease, the patient's echocardiography revealed large atrium sizes, slightly thick mitral valves, hypokinetic interventricular septum, akinetic inferior and posterior walls, biventricular hypertrophy, and global longitudinal strain as 3.1%. All these findings supported an infiltrative cardiac involvement.

In the detailed examination of the patient for further organ involvements associated with Fabry disease, no skin findings like angiokeratoma or ophthalmologic pathology were observed. He also did not experience frequent extremity pain or periodic pain crises. He had no history of cerebrovascular accidents.

The patient who had impaired hearing in his late 40s had undergone an audiometric examination, which was reported

as mild conductive hearing loss and diagnosed as idiopathic. The audiometric examination done in our study showed mild bilateral sensorineural hearing loss. Because it was decided that the existing renal and cardiac involvements would not benefit from enzyme replacement therapy, enzyme replacement therapy was not started.

After the diagnosis of Fabry disease, family screening was made for the patient's family. The disease was found in the patient's uncle aged 74 years, and two male and one female cousins aged 38, 35, and 34 years, respectively. The uncle had proteinuria, stage three chronic kidney disease, and heart failure. Enzyme therapy was not initiated due to his age and the progression of the disease. The patient's two male cousins had asymptomatic proteinuria and pain crises. The female cousin was asymptomatic, her cardiac and renal examinations were normal. The two male cousins were started on enzyme therapy. There were consanguineous marriages between the patient's mother and father and between the mothers and fathers of their cousins who had the disease. The mother of the patient had died of renal failure at a young age. Also, although the cause was not fully understood, his grandmother had died at an early age. The patient's family pedigree is given in Figure 2.

Index Case-2

This patient was a 54-year-old female. She was included in the study due to the detection of mild unilateral sensorineural hearing loss. She had no known history of illness nor was she taking any medication. There was no family history of renal failure, heart failure, or cerebrovascular accident. Her brother had hearing loss at the age of 30. Her renal functions and echocardiography were normal. No proteinuria was detected in the urine. No pathologies were detected in the eye and skin examinations. There were no symptoms of painful crisis, abdominal pain, or decreased sweating. Mild sensorineural hearing loss was the only finding associated with Fabry disease in the patient. The patient's family could not participate in the Fabry Disease screening due to the coronavirus disease-2019 pandemic outbreak.

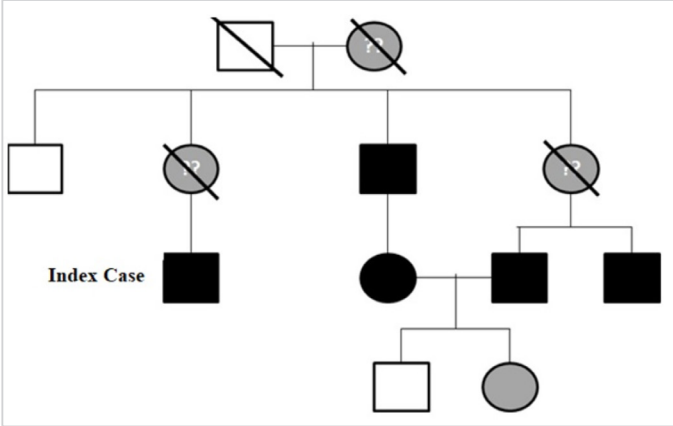

Figure 2. Family pedigree of the male patient diagnosed with Fabry disease at the end of the study

Discussion

Presently, there are no exact data for Fabry disease incidence in Turkey. In this study, Fabry disease was found in 1.2% (2/168) of our study cohort. Although two of the study patients were diagnosed, four more were diagnosed with Fabry disease in family screenings. Although Fabry disease is evaluated in the rare group of metabolic diseases, we believe that this frequency might be significantly higher since our study was conducted with a specific group of patients and in a country where consanguineous marriage is common. To obtain healthier data, multi-center studies that support these findings should be conducted with more patients. Achieving similar results in a larger population would guide the development of Fabry disease screening programs.

As mentioned above, enzyme replacement therapy was not given to the male patient, but the two family members diagnosed in family screening had early diagnoses of renal and/or cardiac involvement, therefore decision was to start them on enzyme replacement therapy. This screening provided the possibility of protecting family members from morbidity caused by Fabry disease as well as the possibility for early diagnosis in the next generations. Previous studies have proved that if enzyme treatment was started by detecting Fabry disease at that time, it may prevent these complications or delayed their occurrence (18-20). So, early diagnosis and treatment of Fabry disease give a chance to prevent disease complications. It makes Fabry disease a disease that may be suitable for screening programs.

In a 2016 study conducted in Turkey, Fabry disease was screened in 1,527 dialysis patients with idiopathic end-stage renal failure and the authors reported to have found low α-GLA activity in 130 (8.5%). In five (0.3%) of these patients, GLA gene mutation was detected, and Fabry disease diagnosis was confirmed (11). In another study conducted with 5,657 end-stage renal disease patients, 17 (0.3%) were diagnosed with Fabry disease (21). This is one of the studies that show the importance of screening for Fabry disease.

Screening studies have also been conducted on cardiac involvement, another complication of Fabry disease. In a study from Turkey which included 80 patients with idiopathic left ventricular hypertrophy, hemizygous mutations associated with Fabry disease were detected in two male patients (2.5% of the screened population) (22). In another study conducted in Japan in 2012, 738 male patients with idiopathic left ventricular hypertrophy were screened for Fabry disease and three (0.4% of the screened patients) were diagnosed (12).

Although sensorineural hearing loss is a common condition in Fabry patients and frequently followed-up as idiopathic,

no screening studies have been reported in this patient group to date. In a 2002 study, Germain et al. (23) investigated the cochlear functions of 22 homozygous male patients with classical Fabry disease and found the prevalence of hearing loss as 54.5%.

In our male patient that was diagnosed with Fabry disease, the absence of characteristic clinical signs of the disease such as angiokeratoma, cornea verticillata, limb pains**,** and acroparesthesia in the presence of sensorineural hearing loss- indicates that the disease has a heterogeneous clinical picture. The absence of any other clinical findings suggests that the presence of idiopathic sensorineural hearing loss alone should be sufficient for screening the disease.

Another noteworthy finding of our study was that although α-GLA enzyme activity was found to be low in 11 male patients, any of the gene mutations associated with Fabry disease was detected in only one patient. According to the current literature, low α-GLA enzyme activity in leukocytes has diagnostic value in male patients (24). Based on the results of our study, we can attribute the inconsistency between enzyme activity measurement and genetic sequencing results to two possibilities. Firstly, measurement of enzyme activity in peripheral leukocytes may be more accurate than the measurement of a sample on dry filter paper. The second is that there may be genetic mutations that have not yet been identified for Fabry disease and therefore cannot be investigated. While there were 429 gene mutations known by 2005, today more than 900 mutations are known (25, 26). This fact also supports the second assumption.

The mutation detected in our female patient who was diagnosed with Fabry disease and did not have clinical findings of the disease was defined as c.937G> T(p.D313Y). This mutation is related to a later-onset milder phenotype than the typical phenotype (27). c.1010T> C(p.F337S) gene mutation was detected in the male patient with the disease.

One of the limitations of our study is the lower number of patients compared to the other studies on Fabry disease screening. Prospective studies with a larger number of patients are needed. The inability to perform family screening of index case 2 due to the pandemic conditions has been another limitation in our study.

Conclusion

Given that Fabry disease was found in 1.2% (2/168) of the patients, our study showed that screening for Fabry disease is a beneficial strategy for detecting new cases in patients with idiopathic sensorineural hearing loss, as Fabry disease should be considered in the differential diagnosis in this group of patients. While one of our cases diagnosed with Fabry disease had sensorineural hearing loss, the absence of characteristic clinical findings of the disease such as angiokeratoma, corneal verticillata, limb pain, and acroparesthesia, supports the idea of using sensorineural hearing loss as the primary parameter in screening.

*The article was created from the corresponding author's thesis of internal medicine specialty.

Ethics Committee Approval: The study was approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (decision no: I1-08-19, date: 25.06.2019) and conducted in line with the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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

Main Points

- This study aimed to screen for Fabry disease in patients with idiopathic sensorineural hearing loss.
- Eighty four female and 84 male patients were included in the study. At the end of the study, a gene mutation associated with Fabry disease was detected in one female patient and one male patient.
- After the family screening, a genetic mutation associated with Fabry disease was detected in four relatives of the male patient.
- This study showed that screening of Fabry disease is a beneficial screening strategy for detecting new cases in patients with idiopathic sensorineural hearing loss and Fabry disease should be considered in the differential diagnosis in this group of patients.

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Do Lymph Node Ratio and Histopathologic Parameters Have Any Prognostic Value in Primary Parotid Gland Carcinomas?

Original Investigation

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Abstract

Objective: To analyze the demographic characteristics and the pathological results of neck dissection in primary parotid gland (PG) cancer patients, and to investigate the effects of histopathological parameters (perineural invasion, lymphovascular invasion, and extracapsular spread), neck metastasis, stage and lymph node ratio (LNR) on survival.

Methods: Patients who underwent parotidectomy for malignant PG tumors between 2000 and 2019 years were retrospectively reviewed from the medical records. Thirty patients who were treated with parotidectomy and neck dissection were included in the study. Lymph node ratio was calculated as the ratio of the number of metastatic lymph nodes (LN) to the total number of excised LNs. Tumor stage, regional LN metastasis, LNR, perineural invasion, lymphovascular invasion, and extracapsular spread were reviewed for the effects on survival with the Kaplan–Meier analysis.

Results: The study included 17 (57%) male and 13 (43%) female patients. Their mean age was 67.93±16.90 years (range, 50–85 years). The average number of the excised LN was 26.03±11.79 (range, 3–50). Mean LNR was 0.16±0.26. The Kaplan–Meier analysis showed that neck metastasis (p=0.001) and LNR (p<0.001) were associated with shorter survival times compared to perineural invasion (p=0.818), lymphovascular invasion (p=0.154), extracapsular spread (p=0.410) and stage (p=0.294). In multivariate COX regression analysis, only LNR had a statistically significant difference (p=0.027) compared to the other parameters.

Conclusion: The present study suggests that LNR and neck metastasis are associated with shorter survival times in PG cancers. Lymph node ratio can be used as a prognostic marker in these patients.

Keywords: Parotid cancer, lymph node metastasis, neck, survival, lymph node ratio

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Cite this article as: *Özcan C, Gür H, İsmi O, Vayisoğlu Y, Bal KK, Bozdoğan Arpacı R, Görür K. Do Lymph Node Ratio and Histopathologic Parameters Have Any Prognostic Value in Primary Parotid Gland Carcinomas?. Turk Arch Otorhinolaryngol 2023; 61(2): 58-65*

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Received Date: 09.04.2023
Accepted Date: 23.05.2023

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DOI: 10.4274/tao.2023.2023-3-5

Introduction

Salivary gland tumors are rare and represent 0.3% of all malignant neoplasia. Malignant salivary gland tumors constitute approximately 3–6% of all head and neck cancers (1). Seventy percent of the salivary gland tumors are seen in the parotid gland (PG) and 17–34% of the PG tumors are malignant (1-4).

While it is well known that the prognosis of head and neck squamous cell carcinomas is largely dependent on lymph node (LN) metastasis, the treatment of neck metastasis in PG carcinomas has received

little attention. There are still controversies on the treatment planning of node-negative neck in PG cancers. Some authors recommend elective neck dissection (END) for malignant PG tumors, whereas others recommend neck dissection for only LN-positive patients or some specific tumor types (5, 6). The rarity, diversity, and heterogeneity of these tumors lead to more complex and complicated treatments.

Lymph node ratio (LNR) is defined as the ratio of the number of positive LNs to the number of total LNs removed with neck dissection. It has been reported that it predicts the survival of patients with head and neck cancers such as oral cavity, larynx, and hypopharynx cancers (7, 8). Metastasis to the LNs of the neck in head and neck cancers generally has significant prognostic importance. The number, laterality, and size of metastatic LNs in the neck are used for staging in salivary gland cancers according to the tumor-node-metastasis (TNM) staging system (9). Extranodal spread of metastasis is also the other factor affecting survival. Lymph node ratio has been indicated to be a newly proposed parameter over staging and survival in salivary gland cancers (10). An increase in the number and ratio of positive LNs is closely associated with increased overall and cancer-specific mortality (11).

In this article, we aimed to analyze patients' demographic characteristics and the clinical and pathological results of neck dissection in primary PG cancer patients. The effects of histopathological parameters (perineural invasion, lymphovascular invasion, and extracapsular spread), neck metastasis, stage, and LNR on the survival of patients were also evaluated and discussed.

Methods

The study was approved by the Clinical Research Ethics Committee of Mersin University (decision no: 2023/193, date: 29.03.2023). Patients who underwent parotidectomy for malignant PG tumors between 2000 and 2019 were retrospectively reviewed from the medical charts. Fifty-nine patients were found to have been operated on for malignant tumors of the PG. Two patients had lymphoma, four patients had metastasis to the PG, and 14 patients had an invasion of the PG by a facial skin and scalp melanoma (two patients) or a squamous cell carcinoma (12 patients); thus, these 20 patients were excluded from the study. Six patients who were treated with parotidectomy alone were also excluded. The remaining 33 patients had undergone parotidectomy and neck dissection. Among these 33 patients, three who had died from causes (one heart attack, one cerebrovascular event, and one liver failure) other than PG cancer were also excluded. Eventually, 30 patients who were treated with parotidectomy and neck dissection were included in our study. Demographic features, clinical examination findings, surgical and histopathologic results, and overall survival times were retrieved from patients' medical charts. Tumor sizes were measured based on the larger diameter of the tumor on histopathological examination. Tumor staging was assessed according to the recent World Health Organization TNM classification of malignant tumors (9). Histopathological results of parotidectomy and neck dissection specimens were analyzed in terms of histopathologic tumor type, tumor grade, metastasis to LNs, extracapsular spread, and lymphovascular and perineural invasion. Lymph node ratio was calculated as the ratio of the number of metastatic LN to the total number of excised LNs. LNRs were categorized into four groups: 0, 0.001–0.1, 0.11–0.5, and >0.5 (12). The number of metastatic LNs was also grouped as 0, 1, 2–4, 5–10, and >10.

Nodal involvement in histopathological results was assessed in terms of age, gender, histopathological grade, T stage, and perineural and lymphovascular invasion. High-grade mucoepidermoid carcinoma, solid-type adenoid cystic carcinoma, adenocarcinoma not otherwise specified, squamous cell carcinoma, salivary duct carcinoma, carcinoma ex pleomorphic adenoma, and undifferentiated carcinoma were accepted as high-grade tumors on final histopathological examination.

Patients were treated with complete superficial, total, or radical parotidectomy and additional neck dissection. Small-sized superficial tumors were removed from the PG with complete superficial parotidectomy, while larger or deep lobe tumors were removed with total parotidectomy. The facial nerve was sacrificed in the presence of preoperative facial paralysis or when the facial nerve was considerably infiltrated by a tumor. After sacrificing the facial nerve, the facial nerve was not reconstructed. Branches of the facial nerve directed toward the eye were preserved as much as possible when the tumor was located in the lower segment of the PG. If there was a high index of suspicion for a malignant parotid tumor in the result of the preoperative examination or the fine needle aspiration biopsy (FNAB), a frozen section was applied. Visible level II LNs during parotidectomy were selected for a frozen section in patients who did not have any clinically preoperative nodal involvement. Neck dissection was considered in patients with suspected malignant tumors when physical examination, imaging methods, FNAB, frozen section and final histopathologic examination (high-grade tumors) were evaluated. An END including levels I, II and III was therefore used in patients without clinically involved LNs in the neck, whereas patients with clinical nodal involvement were treated with modified radical neck dissection or radical neck dissection. According to the final histopathological report of the parotidectomy material, patients who did not accept neck dissection with a second operation were referred to radiation oncology and/or medical oncology if deemed necessary. The need for radiotherapy (RT) ± chemotherapy (CT) after histopathological examination of the specimens of parotidectomy and neck dissection was also evaluated by the Head and Neck Cancer Board.

Tumor stage, regional LN metastasis, LNR, perineural invasion, lymphovascular invasion, and extracapsular spread were reviewed with Kaplan–Meier analysis for their effects on survival.

Statistical Analysis

Statistical analysis was done with SPSS version 23 (SPSS., Inc, IBM, Armonk, NY). Data were shown as mean ± standard deviation for continuous variables and the number of cases was used for categorical ones. Data were reviewed for normal distribution using the Shapiro–Wilk test. Disease-specific survival times were calculated for each patient. The Kaplan–Meier survival analysis was used to evaluate LN metastasis, LNR, perineural invasion, perivascular invasion, extracapsular spread, and stage on survival of the patients. A COX regression analysis was also done to assess the effects of multiple independent variables on survival status. A p-value of <0.05 was considered statistically significant.

Results

In our study, there were 17 (57%) male and 13 (43%) female patients. Their mean age was 67.93±16.90 years (range, 50–85). Fourteen patients had the tumor on the right-side PG and sixteen had the tumor on the left-side PG. Mean tumor size was 39.16±18.31 mm. Patients had undergone superficial parotidectomy (eight patients), total parotidectomy (five patients), or radical parotidectomy (17 patients).

Histopathological results demonstrated that the most common tumors in the PG were mucoepidermoid carcinoma, adenoid cystic carcinoma, and squamous cell carcinoma, respectively. The distribution of the remaining tumor types is given in Table 1.

When T stages were reviewed, 14 patients had an early-stage tumor (T2) and 16 had an advanced-stage tumor (T3 and T4). Fourteen patients (46.7%) had no positive LN (N0) and 16 patients (53.3%) had metastasis to the regional LNs, with N1 in five and N2 in 11 patients (Table 2). Patients with metastatic LNs had high-grade malignancies except for one patient with adenoid cystic carcinoma (cribriform pattern). When the relation between T stage and regional metastasis was reviewed, metastasis rates were 42.8% in T2, 100% in T3, and 50% in T4. The 5-year disease-free survival rates were 28.6% in T2 tumors, 25% in T3 tumors, 16.6% in T4 tumors, and 23.3% overall.

Table 1. Distribution of the histopathological diagnosis of the patients

Histopathology	n=30
Mucoepidermoid carcinoma	
Low-grade	1
High-grade	9
Adenoid cystic carcinoma	5
Squamous cell carcinoma	5
Adenocarcinoma, NOS	2
Salivary duct carcinoma	3
Acinic cell carcinoma	1
Sebaceous adenocarcinoma	1
Carcinoma ex pleomorphic adenoma	1
Polymorphous low-grade adenocarcinoma	1
Undifferentiated carcinoma	1

n: Number of patients, NOS: Not otherwise specified

The average number of the excised LN was 26.03±11.79, range 3–50. The mean number of excised metastatic nodes was 3.46±5.65, range 1–19. Mean LNR was 0.16±0.26. Patients' LNR and the number of positive LN are shown in Table 3. Occult metastasis rate was 20% and these patients had mucoepidermoid carcinoma (three patients), adenoid cystic carcinoma (one patient), salivary duct carcinoma (one patient), and undifferentiated carcinoma (one patient).

The Kaplan–Meier analysis revealed that positive neck metastasis (p=0.001) (Figure 1) and LNR (p<0.001) (Figure 2) were associated with shorter survival times compared to perineural invasion (p=0.818), lymphovascular invasion (p=0.154), extracapsular spread (p=0.410) and stage (p=0.294).

In multivariate COX regression analysis, only LNR showed a statistically significant difference (p=0.027) compared to the other parameters, with neck metastasis (p=0.625), perineural invasion (p=0.185), lymphovascular invasion (p=0.505), extracapsular spread (p=0.971), and stage (p=0.787) (Table 4).

Discussion

The most common PG tumors were mucoepidermoid carcinoma, adenoid cystic carcinoma, and squamous cell carcinoma in our study. The 5-year disease-free survival rates were 28.6% in T2 tumors, 25% in T3 tumors, 16.6% in T4 tumors, and 23.3% overall. We found the mean LNR as 0.16±0.26. The occult metastasis rate was 20%. Sixteen patients (53.3%) had metastasis to the cervical LNs. The COX regression analysis suggested that LNR could be associated with survival in PG cancers. Based on Kaplan–Meier analysis, we found that LNR and neck metastasis had a negative effect on survival rates.

The PG is the largest salivary gland and houses a vast majority of neoplastic masses in the salivary glands. The nature of neoplastic masses in the PG is predominantly benign rather than malignant. Malignant salivary gland tumors are also mostly seen in the PG and the most common malignant PG tumor is mucoepidermoid carcinoma (2). Like other head and neck cancers, they tend to be seen more commonly in older and male patients.

Table 2. Histopathologic tumor type, T, N, and M stages, RT/CT treatment and survival times of the patients who underwent parotidectomy and neck dissection

					Lymph node			
P.no	**Histopathological type**	**T stage**	**N stage**	**Metastasis**	**Metastatic**	**Reactive**	**Postoperative RT/CT**	**Survival (months)**
1	Adenoid cystic carcinoma	T2	N0	-	-	42	RT + CT	106 (alive)
2	Squamous cell carcinoma	T3	N2b	-	7	29	RT + CT	2
3	Adenoid cystic carcinoma (solid)	T4b	N1	-	2	18	RT + CT	33
4	Adenocarcinoma, NOS	T2	N0	-	-	6	CT	22
5	Squamous cell carcinoma	T4a	N0	-	-	18	RT + CT	68 (alive)
6	Mucoepidermoid carcinoma (high grade)	T4a	N2b	-	3	20	-	15
7	Squamous cell carcinoma	T3	N2b	-	5	12	RT	3
8	Mucoepidermoid carcinoma (high grade)	T2	N2b	-	19	-	RT	10
9	Adenoid cystic carcinoma	T2	N0	-	-	37	-	3
10	Salivary duct carcinoma	T4a	N2b	-	18	8	-	66
11	Mucoepidermoid carcinoma (high grade)	T4a	N2b	-	7	18	-	1
12	Mucoepidermoid carcinoma (high grade)	T4a	N0	-	-	31	-	55
13	Acinic cell carcinoma	T2	N0	-	-	28	-	76
14	Mucoepidermoid carcinoma (high grade)	T3	N1	-	1	31	-	84
15	Sebaceous adenocarcinomas	T4a	N0	-	-	28	-	6
16	Mucoepidermoid carcinoma (high grade)	T4a	N0	-	-	41	RT + CT	14
17	Mucoepidermoid carcinoma (low grade)	T2	N0	-	-	47	RT	125 (alive)
18	Mucoepidermoid carcinoma (high grade)	T2	N2b	-	6	11	CT	15
19	Salivary duct carcinoma	T4a	N2b	-	19	4	RT + CT	24
20	Squamous cell carcinoma	T4a	N0	-	-	33	-	17 (alive)
21	Mucoepidermoid carcinoma (high grade)	T2	N1	-	1	49	RT + CT	3
22	Salivary duct carcinoma	T2	N1	-	1	2	-	25
23	Squamous cell carcinoma	T2	N0	-	-	21	-	46
24	Adenoid cystic carcinoma (cribriform)	T2	N0	-	-	26	RT + CT	49 (alive)
25	Adenocarcinoma, NOS	T3	N2b	-	5	17	RT + CT	8 (alive)
26	Adenoid cystic carcinoma (cribriform)	T4a	N2b	-	5	11	RT	7 (alive)
27	Mucoepidermoid carcinoma (high grade)	T4a	N0	-	-	11	RT	4 (alive)
28	Carcinoma ex pleomorphic adenoma	T2	N2b	-	4	42	CT	29
29	Polymorphous low-grade adenocarcinoma	T2	N0	-	-	24	RT	107 (alive)
30	Undifferentiated carcinoma	T2	N1	-	1	12	-	23 (alive)

CT: Chemotherapy, P. no: Patient number, RT: Radiotherapy

Table 3. Classification of LNRs of patients with a node-positive neck

LNR (mean: 0.13)	**Number of patients (%) n=30**
0	14 (47%)
0.001–0.1	5 (17%)
0.11–0.5	8 (26%)
>0.5	3 (10%)
Positive lymph node	
0	14 (47%)
1	5 (17%)
2–4	2 (6%)
5–10	6 (20%)
>10	3 (10%)

LNR: Lymph node ratio, n: Number of patients

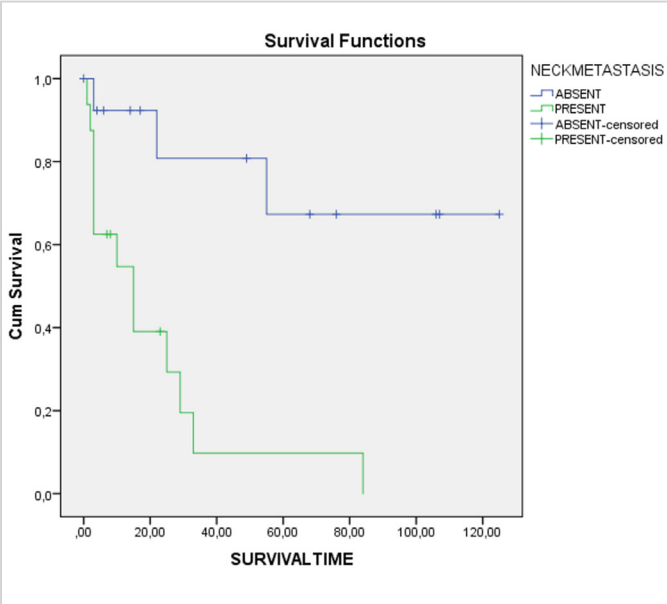

Figure 1. Kaplan–Meier survival analysis as to whether neck metastasis is present or absent

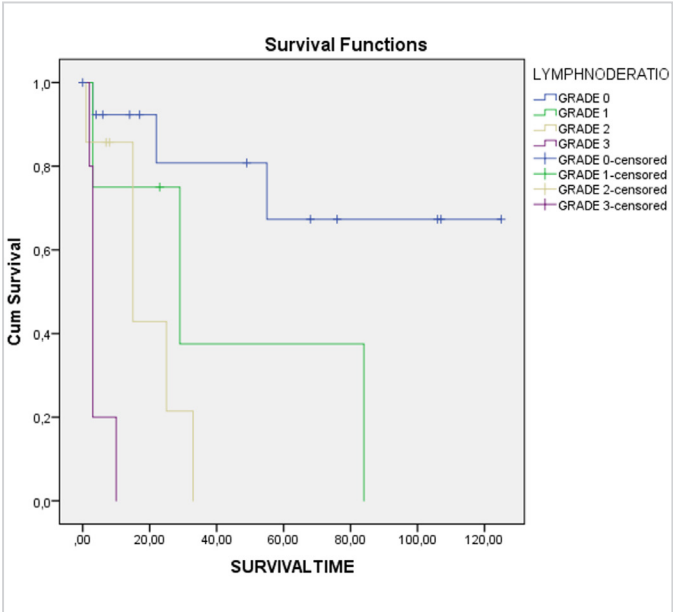

Figure 2. The effect of lymph node ratio in Kaplan–Meier survival analysis

Neck dissection plays an important role in the management of malignant head and neck tumors and it is well-known that neck metastasis significantly reduces the survival rates of patients. LN-positive neck with PG cancers requires therapeutic neck dissection as a part of treatment, but the approach to LN-negative neck with primary parotid cancers remains unclear regarding END. Elective neck dissection is not recommended routinely for all LN-negative necks in primary PG cancers except for the high risk of neck metastasis. Primary PG cancers are relatively uncommon and they have numerous histopathologic subtypes. Therefore, deciding on and planning for neck dissection for each histopathological subtype of primary PG cancer can be difficult. High-grade tumors and high T (T3/T4) stages have been shown to have a higher risk for metastasis to the neck and may need an END if the neck is clinically N0 (cN0) (13, 14). On the other hand, observation without END after parotidectomy may be sufficient in patients under the age of 60, T1 and T2 tumors, and low-grade tumor histology in cN0 necks (6). Occult neck metastasis rates have been suggested to be 12–48% (15-18). Additionally, the histological grade and final pathological diagnosis of the tumor can usually not be detected before the surgery. Therefore, deciding about END can remain a controversial issue. Fine needle aspiration biopsy and peroperative frozen section may give information about malignant versus benign tumor histology. The occult metastasis to level II LNs is more common than other neck levels and the detection of metastasis to level II or periparotid LNs on frozen section biopsy or FNAB may indicate the need for neck dissection (19). So, these two entities may prevent unnecessary neck dissections by distinguishing malignant tumors from benign ones. High-grade tumor histology after parotidectomy without neck dissection in cN0 neck may require a second operation for neck dissection. The occult metastasis rates of PG cancers are 4.3% in T1 or T2 tumors, 35% in T3 or T4 tumors, 6.1% in low or intermediate-grade tumors, and 24.2% in high-grade tumors in cN0 patients (20). Also, occult nodal disease occurs in 13.6% of cN0 patients (20). In our study, we performed an END in high-grade tumors, T3 and T4 tumors, and positive level II or periparotid LNs on FNAB or frozen section biopsy. The most common malignant primary PG tumor was mucoepidermoid carcinoma, followed by

Table 4. Multivariate COX regression analysis of various parameters over disease-specific survival

				95.0% confidence interval for β	
Parameter	**β**	**Standard error**	**p-value**	**Lower bound**	**Upper bound**
Neck metastasis	0.595	1.217	0.625	0.167	19.700
Lymph node ratio	1.067	0.484	0.027	1.126	7.499
Extracapsular spread	-0.033	0.893	0.971	0.168	5.567
Stage	-0.167	0.616	0.787	0.253	2.831
Perineural invasion	-0.922	0.695	0.185	0.102	1.555
Lymphovascular invasion	0.405	0.608	0.505	0.456	4.934

adenoid cystic carcinoma and squamous cell carcinoma in our study. We found that occult metastasis rates were 20% in our patients.

Histopathological results of surgical specimens may show the survival of patients with PG cancer. Histopathological factors associated with poor prognosis have been clearly known for decades. These factors are high-grade tumors, and perineural and lymphovascular invasion, as well as metastasis to regional LNs, especially with extracapsular invasion, and closely associated with low survival rates. For these reasons, high N stages, two or more metastatic LNs, and extracapsular spread may require postoperative adjuvant RT. Many studies have shown the effects on survival of the number of metastatic LNs. When the number of metastatic LNs increases in patients with major salivary gland cancers, cancer-specific survival decreases (21). LNRs have also been suggested to be closely related to the life expectancy of major salivary gland tumor patients (22). Higher LNR in minor salivary gland cancers has been reported to be associated with shorter survival times (23). Debates over the impact on the survival of LNR are ongoing and LNR values >0.15–0.38 have been shown to be associated with poor prognosis (11, 21, 23, 24). However, Hong et al. (25) found a cutoff value of 4.0 for LNR in high-grade salivary gland cancers. LNR could be affected by the numbers of both metastatic and non-metastatic LNs in neck dissection materials. When the number of metastatic LNs is high or the number of non-metastatic LNs is low in neck dissection materials, LNR may be expected to be a higher number. The extension of END can change LN numbers in occult neck metastases. Clinically and radiologically evident metastatic LNs may show that the LNR will be higher. A metastatic LN number greater than four is also associated with poor prognosis (21). Furthermore, the LNR and the number of metastatic LNs can be predictive of the need for postoperative RT after parotidectomy along with neck dissection. Similar to other studies, we suggest that LNR has a negative impact on survival in primary PG cancers.

Aro et al. (10) proposed a new classification system for nodal staging based on the number of metastatic LNs in salivary gland cancers. They divided the numbers of metastatic LNs into three groups as N1: one to two LNs, N2: three to 21 LNs, and N3: 22 or more LNs. Lee et al. (11) proposed another N staging system based on the numbers of positive LNs, where node negative is N0, one positive LN is N1, and ≥ two positive LNs or extracapsular extension is N2.

Some histologic factors can provide information about tumor aggressiveness, such as perineural invasion, extracapsular extension, and lymphovascular invasion that can cause locoregional recurrences and poor prognosis (26, 27). At the same time, these histologic factors require postoperative adjuvant therapies (RT ± CT) (27). Histopathological grade and preoperative facial paralysis can be significant predictors for occult metastasis in cN0 patients (28). Histopathologically positive nodes (pN+) can occur in 77–87% of clinically node-positive LNs (cN+) (6, 28).

Most of the studies about LNR have used data from Surveillance, Epidemiology, and End Results due to the rarity of primary PG cancers (21, 29). Hong et al. (25) suggested that the median number of total excised LN and metastatic LN were 27 (range, 1–135) and two (range, 0–68), respectively, in salivary gland cancers. Their series included I–III or I–IV elective and therapeutic neck dissections. They found a significant association between LNR and overall survival. High LNR may be related to shorter disease-specific, disease-free, and overall survival (23). The number of excised LNs >18, the number of positive LNs >4, and the LNR >33.33% are associated with poor prognosis (24). Lei et al. (29) proposed four risk groups (R0, R1, R2, and R3) based on LNR cutoff points, which were ≤0.17 in R1, 0.17–0.56 in R2, >0.56 in R3 and 5-year cause-specific survival was 88.6% in R0, 57.2% in R1, 53.1% in R2 and 39.7% in R3.

The present study has some limitations. These limitations are being a single-center study, having a small patient population, and its retrospective nature.

Conclusion

The present study suggests that LNR and neck metastasis are associated with shorter overall survival times in PG cancers. Lymph node ratio may be used as a prognostic marker in patients with PG cancer. Our results should be supported with larger prospective studies for more detailed prognostic information about primary PG cancers.

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Mersin University (decision no: 2023/193, date: 29.03.2023).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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

Main Points

- The higher number of metastatic lymph nodes in primary parotid gland cancers may be associated with poor prognosis.
- Higher lymph node ratios may be associated with lower 5-year survival rates.
- Neck metastasis in primary parotid gland cancers may be associated with a shorter life expectancy.
- Neck dissection along with parotidectomy provides information about histopathological parameters (e.g., neck metastasis, lymph node ratio).
- Given the rarity of primary parotid gland cancers, the lymph node ratio needs to be supported by further studies in larger patient populations.

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Efficacy of the DoctorVox Voice Therapy Technique for the Management of Vocal Fold Nodules

Original Investigation

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Abstract

Objective: Vocal fold nodules (VFNs) are among the most common causes of dysphonia. Phonolaryngeal microsurgery, pharmacological treatments, and voice therapy (VT) have been used for treating VFNs. VT has been advocated as the primary treatment of choice. This study investigated the efficacy of the DoctorVox Voice therapy technique (DVT) for treating VFNs.

Methods: A total of 38 patients with VFNs and 40 individuals without any voice problem (control group) were included. All patients received the DVT program. Otorhinolaryngology examination, videolaryngostroboscopy (VLS), and acoustic analysis (SPL, mean F0, jitter %, shimmer %, NHR) were performed at pretreatment, one and six months after the end of treatment. The voice handicap index-10 (VHI-10) and the GRB scales were used for perceptual voice evaluation. GRB and VLS scorings were done blindly.

Results: Compared with the pretreatment values, the first- and the sixth-month values after treatment demonstrated a significant decrease in VHI-10 (19.5 vs. 5.1), GRB (2.3 vs 0.68 for G value) and VLS scores, SPL (54.4 vs 66.1 dB), F0 (201 vs. 227 Hz), jitter % (1.46 vs 0.85), shimmer % (3.27 vs 2.51), NHR (1.15 vs. 0.46) values among patients. Most of the voice parameters in the sixth month after the DVT program did not differ significantly from those of the control group.

Conclusion: The DVT was found to be an effective method in VFN treatment.

Keywords: Vocal folds, dysphonia, voice disorder, treatment outcome, laryngeal diseases, therapy

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Cite this article as: *Denizoğlu İ, Şahin M, Şahin Orhon E. Efficacy of the DoctorVox Voice Therapy Technique for the Management of Vocal Fold Nodules. Turk Arch Otorhinolaryngol 2023; 61(2): 66-74*

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Received Date: 19.10.2022
Accepted Date: 17.05.2023

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DOI: 10.4274/tao.2023.2021-11-1

Introduction

Vocal fold nodules (VFNs) are benign lesions of the vocal folds (VF) caused by repetitive microtrauma to the vocal fold mucosa leading to histological changes and concomitant dysphonia (1). VFNs are common causes of hoarseness in the population and cause labor loss and deterioration in quality of life. The main symptoms are hoarseness, throat discomfort, and vocal fatigue (2). Vocal overuse, misuse, abuse, and imbalances/increases in laryngeal muscle tension were pointed out as the main causative factors (1,2). Non-voice-use-related causative factors could be laryngopharyngeal reflux, smoking, and allergy (2,3). VFNs are more commonly diagnosed in women in adulthood. VFNs are mostly seen in the mid-membraneous part of the VF mucosa where maximum impact stress occurs (3). Irregular closure of VFs creates valve inefficiency, and consequently, a compensatory reaction can cause hyperfunctional behavior in the supraglottic structures and extrinsic laryngeal muscles.

There is no Level 1 evidence as to which method is effective for treating patients with VFN (4). A Cochrane review reported evidence from non-randomized interventional studies (Levels 2-4) only (5). In daily clinical practice, most clinicians prefer voice therapy (VT) as the primary method (2,4). The evidence base for the effectiveness of VT is constantly evolving (4,6). Laryngeal microsurgery (LM) is considered in a limited number of selected patients and in patients that do not respond to VT (5). Different conservative approaches and VT techniques have been described in the literature. However, there is a lack of documentation on the efficacy of different VT techniques. Moreover, there are no algorithms or guidelines available that identify the optimal intensity or duration of VT for VFNs (6-9).

Phonation into resonance tubes is a method known since the 1960s when Professor Sovijärvi introduced glass tubes (10). Voice pathologist Sihvo presented the silicone tube with the LaxVox exercise. The DoctorVox voice therapy technique (DVT) was developed based on Sihvo's LaxVox tube exercise by Denizoglu et al. (11). It is a holistic approach and a direct method that changes the vocal mechanism. Artificially elongated vocal tract and backpressure are the main factors that intuitively balance simultaneous functions included in voice production. DVT is a multi-dimensional, multi-level treatment program (12). Three dimensions (clinician's action plan, exercise patterns, and monitoring) and four levels (preset, exploration, development, and adaptation) are distinguished through DVT practice (Figure 1). The effectiveness of DVT for the management of VFNs was evaluated for the first time in the literature in this study.

Methods

This study was conducted in a voice clinic of a university hospital and approved by the Institutional Review Board of the Local Ethics Committee of Aydın Adnan Menderes University (decision number: 2017/238). The initial examinations of the patients who had been referred to the vocology unit were performed by the same laryngologist and a routine follow-up form for patients with voice disorders was completed. This form includes the patient's demographic, medical, and voice habituation history, as well as vocal assessment, videolaryngostroboscopy (VLS), and voice analysis data.

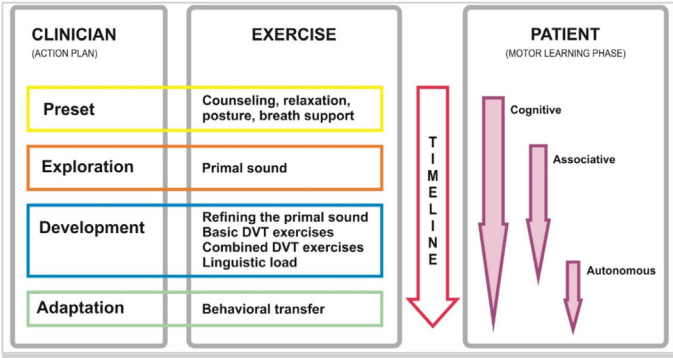

Figure 1. Three levels of DoctorVox voice therapy technique

Participants

Patients diagnosed with VFNs were informed about the disease and the available treatment methods for VFN. The exclusion criteria were: Age <18 years; presence of voice symptoms for less than three months; previous history of a medical condition causing dysphonia, such as neurological, psychiatric, respiratory, endocrine, or autoimmune diseases; history of previous LM, head and neck trauma, radiotherapy, chemotherapy, VT, or vocal training. Those who needed reflux treatment were not included in the study. Patients with any vocal fold pathologies other than VFNs such as vocal fold polyps, cysts, and sulcus vocalis found in the examination were excluded. Patients with irregular pre- and post-treatment follow-up visits, irregular attendance, and follow-up records were also excluded. 40 individuals without any voice problem (control group) were included. The control group was selected from volunteers over 18 years of age, who did not have any complaints about the voice, and whose otorhinolaryngology and voice examinations were normal, with age and gender distribution compatible with the nodule group. The same parameters as the nodule group were recorded

Outcome Measures

Voice-related data from the time of diagnosis, and one month and six months after the end of the DVT were analyzed. The same data was also obtained for the control group. All participants showed their professional voice use and vocal overuse on a 10-mm visual analog scale. The validated Turkish version of the voice handicap index-10 (VHI-10) was used for subjective self-reporting of the severity of vocal symptoms. GRB scale (a version of GRBAS) was used for auditory perceptual assessment. GRB is a reliable and valid scale consisting of three parameters (Grade, Roughness, Breathiness) on a scale of 0–3 (0 is normal, 1 is slight, 2 is moderate, and 3 is a high degree of severity) (13). Voice recordings were separately scored by two experienced otolaryngologists, GRB scorings were done blindly. A paragraph in Turkish composed of 219 words with rich and balanced phonemes was used to record speech. The compatibility between evaluators was analyzed before the study. The intraclass correlation coefficient for the interjudge evaluation was 0.82.

VLS (Karl Storz Pulsar GmbH&Co. KG, Tuttlingen, Germany) was performed to evaluate vocal fold movements and mucosal waveform pattern. The shuffled VLS recordings were separately analyzed by two experienced otolaryngologists. VF dynamics based on VLS were scored using the protocol of the European Laryngological Society.

The basic parameters of this VLS scale were glottal closure, regularity, mucosal wave, and symmetry. VLS was graded using a four-point grading scale (0= no deviance and 3= severe deviance, with 12 max total scores) (14). The compatibility between evaluators was analyzed pre-study. VLS scorings were done blindly and the intraclass correlation coefficient for the interjudge evaluation was 0.79.

Voice samples were recorded via a high-quality unidirectional condenser microphone (AKG, Vienna, Austria) in a sound-insulated room. Each patient was allowed a period to familiarize themselves with the text before recording. The subjects were instructed to phonate sustained vowel [a] at a habitual pitch and comfortable loudness. The task was repeated three times and each trial was captured on a hard disk at a 44.100-Hz sampling rate and 16-bit resolution. Dr. Speech (Tiger Electronics, Inc., WA, USA) software (Vocal Assessment, Real Analysis) for Windows (Version 4.30, MA, USA) was used to capture and analyze the voice samples. "The first and the last one second of the analyzed voice sample were excluded". The mean values were then calculated for each subject. Acoustic parameters, namely, mean fundamental frequency (F0), sound pressure level (SPL), jitter percentage (Jitt %), shimmer percentage (Shim %), noise-to-harmonic ratio (NHR) were obtained. Maximum phonation time (MPT) was measured three times and mean duration was noted.

Treatment

VT was performed by the same experienced phoniatrician. None of the patients were given pharmacotherapy.

The DVT procedure applied for VFNs was:

1. Counseling: The disorder was explained in detail. VLS images were shown and glottic closure was described.

2. Proper abdominodiaphragmatic breathing and posture were studied and using the DoctorVox device, the primal sound was explored (15).

3. Pneumophonic concordance was developed for the first few sessions with homework exercises at low pitches. When the appropriate glottic closure pattern was mastered by the patient with the primal sound, this vocal skill is was transferred to other tasks. The backpressure level was decided empirically between 3 and 7 cm H_2O. The intraoral air pressure was formerly measured by adjusting a pressure sensor (Keller PR-4, Winterthur Switzerland). The clinician increased the backpressure by water depth and the DC-Valve (which has been devised for DVT exercises) until a full chest sound was heard.

4. Treatment at the fourth DVT level was done in the clinic and at home both with reading-speaking-singing tasks; and ten sessions of therapy within an average of 6–8 weeks was given. Each session lasted approximately 25 minutes. The first five sessions were held twice a week, then the patients were called in weekly.

5. When the patient acquired the motor skill for proper glottic closure, an oral mask was used. Oral mask was used while reading, speaking, and singing (water level was less than 5 cm H_2O).

6. The new skill was transferred to behavior by sustaining phonation without the device. Patients were motivated to use their new vocal images in their natural environment. The exercise rate was reduced, the patients intentionally used exercises when they had to remember the ideal phonatory habits.

7. In the consultation and control period, patients were given maintenance exercises and no additional therapy sessions were demanded after the conclusion of therapy. The maintenance exercises mainly focused on keeping the primal sound idea active and included warm-up tasks.

Statistical Analysis

The IBM SPSS Version 20.0 software was used for statistical analysis (IBM Corp., Armonk, NY, USA). Mean, standard deviation, frequency, and ratio values were used in the descriptive statistics of the data. The normal distribution of quantitative variables was assessed with the Kolmogorov-Smirnov test. The differences at different periods among the patients were assessed with a paired sample t-test. The independent t-test was used to assess the differences between the two groups. The numerical results were submitted as a mean ± standard deviation. In all statistical analyses, $p \leq 0.05$ was considered to represent a statistically significant difference.

Results

A total of 46 patients and 40 healthy individuals were included. Eight patients were excluded due to incomplete data. The data of 78 individuals (38 patients, 40 controls) were evaluated. Patient and control group participants were female. None of the patients had a history of LM. Basic data, i.e., age, dysphonia duration, smoking, and habitual voice use are shown in Table 1. There were no significant differences between the patient and the control groups in terms of age and smoking. Occupational voice use and vocal overuse scores were significantly higher in the nodule group.

Voice evaluation and analysis data of the patient and control groups before, in the first and sixth months after therapy are presented in Table 2. The F0, SPL, VHI-10 and MPT values of the patient and control groups before and after the treatment are shown in Figure 2.

The p-values of the statistical differences between the patients' voice-related data from three different times are shown in Table 3.

Table 1. Demographic and voice-related features

		VFN (38)	Control (40)	p
Age	(Years)	29.8±5.3	28.3±2.6	0.873
Dysphonia duration	(Months)	13.5±7.2	n/a	-
Occupational voice use (VAS)	(mm)	8.6±2.4	0.2±0.1	**<0.001**
Vocal overuse (VAS)	(mm)	8.5±3.1	1.7±0.4	**<0.001**
Smoking	Yes (%)	26.4	28.6	0.658

VFN: Vocal fold nodule, VAS: Visual analog scale, p≤0.05 refers to statistical significance

Table 2. Voice-related data of all individuals from three different periods

	Pre-treatment	Post-treatment 1st mo	Post-treatment 6th mo	Control group
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
VHI-10	19.52±7.44	6.22±3.14	5.18±2.69	0.73±0.61
G	2.32±1.68	0.79±0.48	0.68±0.44	0.21±0.3
R	0.93±0.67	0.55±0.64	0.52±0.6	0.11±0.28
B	1.46±0.5	0.44±0.55	0.41±0.52	0.13±0.4
F0 (Hz)	201.9±31.8	227±25.9	232±28.7	234.7±23.1
SPL	54.4±7.9	64.3±8.3	66.1±7.6	66.6±4
% Jitt	1.46±0.24	0.83±0.39	0.85±0.43	0.61±0.27
% Shimm	3.27±1.01	2.46±0.98	2.51±1.14	2.19±0.48
NHR	1.15±0.42	0.48±0.41	0.46±0.35	0.13±0.19
MPT	12.6±4.2	17.4±2.6	17.9±3.1	17.5±2.4
VLS_g	2.14±0.81	0.45±0.58	0.53±0.46	0.26±0.4
VLS_r	0.46±0.42	0.09±0.21	0.08±0.17	0.02±0.1
VLS_m	0.88±0.47	0.25±0.36	0.27±0.45	0.02±0.1
VLS_s	0.17±0.38	0.05±0.2	0.05±0.2	0.02±0.1

mo: Month, VHI-10: Voice handicap index-10, F0: Mean fundamental frequency, SPL: Sound pressure level, % Jitt: Jitter percent, % Shim: Shimmer percent, NHR: Noise-to-harmonic ratio, MPT: Maximum phonation time, VLS: Videolaryngostroboscopy (g: Glottal closure, r: Regularity, m: Mucosal wave, s: Symmetry). Values are expressed as mean ± SD, SD: Standard deviation

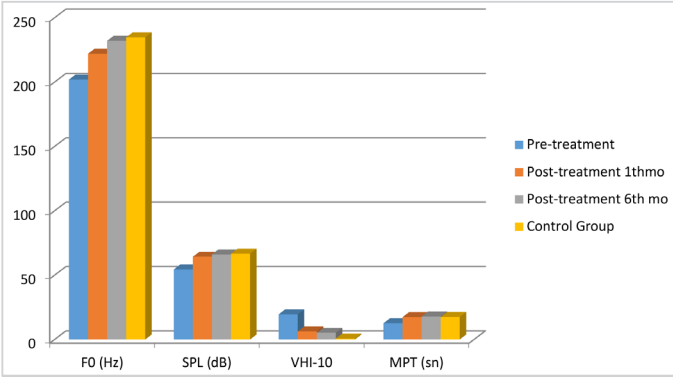

Figure 2. F0, SPL, VHI-10 and MPT values of the patients before and after the treatment and of the control group

F0: Mean fundamental frequency, SPL: Sound pressure level, VHI-10: Voice handicap index-10, MPT: Maximum phonation time

The p-values of the statistical difference between the patients' voice-related data from three different times and the data of the control group are shown in Table 4.

The VHI-10 score, which was 19.5 in the patient group before therapy, was 6.2 in the first month after therapy and 5.1 in the sixth month. The VHI-10 score was found to have statistically significantly decrease after DVT (p<0.001). In patients with VFN, the VHI-10 score (5.1) in the sixth month after DVT was statistically significantly higher (p=0.001) than that of the control group (0.73).

Related to GRB scale, patients' G, R, and B score values had decreased significantly after DVT. The G, R, and B scores of the patients before and after the treatment and the control group are shown in Figure 3. While there was no significant difference between patients' post-treatment G score values and that of the control group, R and B scores were significantly higher in the patients with VFN for all measurements (p=0.218 and 0.189 respectively).

F0, SPL and MPT values of the patients were found to be significantly increased after DVT (Table 3). The F0, SPL and MPT values of the patients in both the first and sixth months after treatment were not significantly different from those of the control group (Table 3).

Patients' % jitters and % shimmer analysis values decreased significantly after the treatment. The % jitter and % shimmer analysis values of the patients in the first and sixth months did not differ significantly from those of the control group (Tables 3 and 4). NHR analysis values of patients with VFN after treatment were significantly higher than those of the

Table 3. The p-values of the significance of the differences between the voice-related parameters of the patients in three different periods of treatment

	I pre vs. post 1st mo	II pre vs. post 6th mo	III post 1st vs. post 6th mos
VHI-10	**<0.001**	**<0.001**	0.624
G	**0.001**	**<0.001**	0.218
R	**0.001**	**0.001**	0.189
B	**<0.001**	**<0.001**	0.742
F0 (Hz)	**0.001**	**0.011**	0.456
SPL	**0.001**	**0.001**	0.345
% Jitt	**0.001**	**0.001**	0.270
% Shimm	**0.001**	**0.002**	0.763
NHR	**<0.001**	**<0.001**	0.345
MPT	**0.001**	**0.001**	0.458
VLS_g	**<0.001**	**<0.001**	0.345
VLS_r	**0.001**	**0.001**	0.463
VLS_m	**0.002**	**0.002**	0.219
VLS_s	**0.002**	**0.002**	0.720

mo/mos: Month/months, I: Pre-treatment vs. Post-treatment 1st month, II: Pre-treatment vs. Post-treatment 6th month vs. Control, III: Post-treatment 1st month vs. Post-treatment 6th month. p≤0.05 refers to statistical significance. VHI-10: Voice handicap index-10, F0: Mean fundamental frequency, SPL: Sound pressure level, % Jitt: Jitter percent, % Shim: Shimmer percent, NHR: Noise-to-harmonic ratio, MPT: Maximum phonation time, VLS: Videolaryngostroboscopy (g: Gottal closure, r: Regularity, m: Mucosal wave, s: Symmetry). Values are expressed as mean ± SD, SD: Standard deviation

Table 4. The p-values of the significance of the differences between the voice-related parameters in three different periods of the data of the patient and control groups

	I Pre- vs. Control	II Post 1st vs. Control	III Post 6th vs. Control
VHI-10	**<0.001**	**0.001**	**0.001**
G	**<0.001**	0.056	0.098
R	**<0.001**	**0.031**	**0.026**
B	**<0.001**	**0.002**	**0.002**
F0 (Hz)	**0.02**	0.166	0.887
SPL	**0.001**	0.09	0.422
% Jitt	**<0.001**	0.237	0.420
% Shimm	**<0.001**	0.224	0.094
NHR	**<0.001**	**0.021**	**0.020**
MPT	**<0.001**	0.643	0.539
VLS_g	**<0.001**	**0.03**	**0.03**
VLS_r	**<0.001**	0.136	0.082
VLS_m	**<0.001**	**0.04**	**0.04**
VLS_s	**<0.001**	0.113	0.327

mo: Month, I: Pre-treatment vs. Control, II: Post-treatment 1st month vs. Control, III: Post-treatment 6th month vs. Control. p≤0.05 refers to statistical significance. VHI-10: Voice handicap index-10, F0: Mean fundamental frequency, SPL: Sound pressure level, % Jitt: Jitter percent, % Shim: Shimmer percent, NHR: Noise-to-harmonic ratio, MPT: Maximum phonation time, VLS: Videolaryngostroboscopy (g: Glottal closure, r: Regularity, m: Mucosal wave, s: Symmetry). Values are expressed as mean ± SD, SD: Standard deviation

control group (Tables 3 and 4). The % jitter, % shimmer, and NHR values of the patients before and after the treatment, and of the control group are shown in Figure 4.

The VLS scale scores were significantly lower in the first and sixth months after treatment compared to pretreatment. VLSg (glottal closure) and VLSm (mucosal wave) scores of patients in the first and sixth months after treatment were significantly higher than those of the control group. There was no significant difference between the VLSr (regularity) and VLSs (symmetry) scores of the patients in the first and sixth months after treatment and the scores of the control group. The VLSg, VLSr, VLSm and VLSs scale scores of the patients before and after treatment and of the control group are shown in Figure 5.

Discussion

VFN formation is a process that causes pathological phonation by disrupting the vibratory characteristics of VFs (14). The initial and primarily preferred method for treating this pathology is VT (15). However, scientific data regarding the effectiveness of VT are still insufficient because of the small number of cases, the lack of control groups, and insufficient data in the follow-up of those who did not receive treatment (16,17). Our study, which has similar deficiencies, is the first in the literature to present that the DVT applied alone is effective for treating VFN.

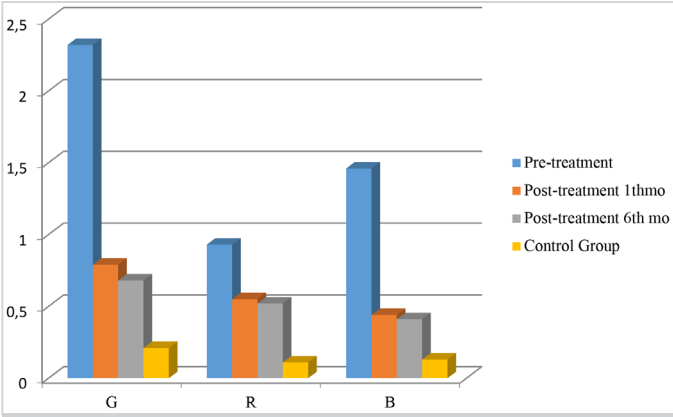

Figure 3. The auditory perceptual assessment of voice quality scores via GRB scale of the patients before and after the treatment and of the control group

G: Grade, R: Roughness, B: Breathiness

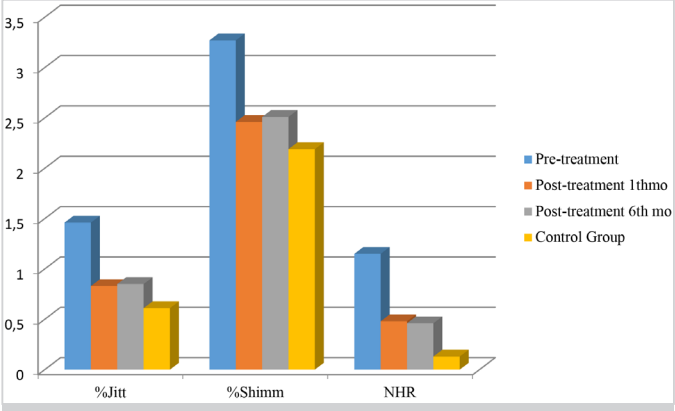

Figure 4. The % jitter, % shimmer and NHR values of the patients before and after the treatment and of the control group

% Jitt: Jitter percent, % Shim: Shimmer percent, NHR: Noise-to-harmonic ratio

In one of the early studies, Verdolini-Marston et al. (1) evaluated thirteen women with VFN before and after therapy, using measurements of phonatory effort, perceptual vocal quality, and vocal fold appearance. Patients who received confidential or resonant VT were compared to a control group of patients who received only vocal hygiene education. The authors found that the two groups that received confidential or resonant VT showed improved voice quality and vocal fold appearance compared to the control group (18). McCrory (19) investigated the records of 26 VFN patients who received combined indirect and direct VT and reported that more than 80% showed normal voice quality or only a mild degree of dysphonia after VT. The author claimed that VT was effective in the elimination of VFNs, restoring normal voice, and improving voice quality. In their study evaluating the effectiveness of resonant VT in 26 female patients with VFN, Saltürk et al. (7) reported VT to be an effective method that provided improvement in both objective and subjective voice parameters. The authors stated that although the study group's VHI-10 scores had significantly decreased after treatment, these scores remained still high in the second month after treatment compared to the control group, indicating that patients continued to experience difficulties in vocal function.

In our study, most of the voice-related parameters in the sixth month after DVT did not significantly differ from those of the control group, but the VHI-10, roughness, breathiness, VLSg, VLSm scores, and NHR values in both the first and

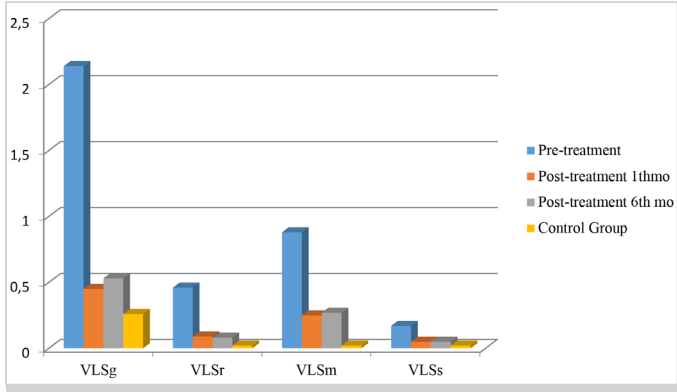

Figure 5. Videolaryngostroboscopic evaluation scores of the patients before and after the treatment and of the control group

VLSg: glottal closure, VLSr: regularity, VLSm: mucosal wave, VLSs: symmetry

sixth months were significantly higher in the patient group compared to the control group. It should be noted that even if significant improvement is achieved after VT, the outcome measures may not return to normal completely, and mild dysphonia may be observed; and these possibilities should be shared with the patient prior to treatment (1,20). In our study, patients were followed up for a longer period than those in McCrory's (19) study. The significant improvement in the voice-related parameters in the first month after the DVT continued through the sixth month, as it was important to show that the efficacy of DVT continued in the next few months in a short program. In addition to the physical effects of the warming-up procedure, patients were urged to warm up their voices in the morning and take a few minutes to correct the primal voice. This behavior is also a psychological motivation for proper voice use.

LM is recommended only when VT is not helpful in VFN treatment (2,4). Murry and Woodson (21) reported that they achieved successful results with VFN via VT and combined the VT and LM methods in selected patients. In our study, LM was not required in any patient.

Béquignon et al. (22) investigated the long-term efficacy of LM alone, and a combination of LM followed by VT in VFN treatment in 60 female and two male patients. The authors reported that recurrent dysphonia was seen in 56% of the patients who did not receive VT and in 22% of those who received VT at a mean time of 5.2 years after LM. The absence of postoperative VT was found significantly associated with a higher dysphonia recurrence. The referred study is important in terms of providing long-term data for the treatment of VFN. There are no data on such long-term outcomes regarding the efficacy of VT in the treatment of VFN. Although the DVT program results after six months were found to be quite satisfactory in our study, further studies on long-term results are required.

Phonation into tubes with one end submerged in water is shown to increase the inertance of the vocal tract. In an inertive vocal tract, phonation threshold pressure decreases, fast-easy opening and closure of the VF is promoted, and maximum flow declination rate increases (23,24). Furthermore, cellular mechanotransduction effects of vibratory backpressure possibly make anatomical changes more prominent. The biofeedback issues in the DVT program increase patient adherence and result in a high rate of the execution of at-home exercise programs.

Holmberg et al. (6) reported that VT had a positive effect on voice quality, vocal status and vocal function for most patients with VFN. We also found similar results in our study as the DVT program is a holistic method including behavioral elements. Especially at the first level of the DVT program and before vocal exercises are started, counseling, relaxation, posture, and breathing issues are reviewed. VT for VFNs must restore the balance between pulmonary support and vibratory forces (25). Holmberg et al. (6) reported that 11 women with VFN showed improvement in various perceptual voice assessment parameters after receiving a behaviorally based VT protocol.

Fu et al. (9) compared the multidimensional outcome results between two VT techniques according to the intensity of treatment in 53 women with VFN. In their study, all patients received one session of vocal hygiene and eight sessions of direct VT. They reported that both treatment methods improved the perceptual vocal quality and acoustic parameters to the same extent. In our study, significant physiological and acoustical results of the DVT supported the efficient clinical use of the VT.

Hyperfunctional vocal behavior in VFN patients can also constrict the supraglottal vocal tract and can suppress optimal VF vibration (26). One of the main goals of VT is to increase the efficient transmission of sound energy by optimizing the resonance characteristics of the supraglottic tract (7,14,27). The benefit of artificial elongation of the vocal tract using resonance tubes, as in DVT practice, is mainly to lower the first formant. This elongation allows the patient to experience the sensory effects of lower phonation threshold pressure, and a lowered average airflow which creates a low-effort voice production (4,28,29).

One of drawbacks of this study was that the number of patients was not high; however it was sufficient for an adequate statistical analysis. Another drawback of our study is that DVT was not compared with different therapy methods. There is a need for large-scale studies that compare larger VFN patient groups managed with different methods such as different VT techniques, vocal hygiene alone, local steroid injection, LM, or follow-up alone (counseling without vocal exercises), and a combination of different methods with follow-up. The strengths of the current study include the relatively long follow-up period when compared to literature and use of multidimensional voice outcome measurements. Besides, the current study is the first one in the literature to present the effectiveness of DVT in VFN treatment for the first time.

Further studies are needed in which different versions of the DVT program are applied, DVT is compared with other VT techniques, and the factors affecting our therapy technique are investigated with a larger group of patients.

Conclusion

VT is essential for treating patients with VFN. This study revealed that DVT significantly improved objective and subjective voice-related parameters in patients with VFNs. We suggest that DVT can be used as an effective method for treating VFNs.

Ethics Committee Approval: This study was conducted in a voice clinic of a university hospital and approved by the Institutional Review Board of the Local Ethics Committee of Aydın Adnan Menderes University (decision number: 2017/238).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.D., E.Ş.O., Concept: İ.D., M.Ş., Design: İ.D., M.Ş., E.Ş.O., Data Collection or Processing: İ.D., M.Ş., Analysis or Interpretation: İ.D., M.Ş., Literature Search: İ.D., M.Ş., E.Ş.O.,N Writing: İ.D., M.Ş., E.Ş.O.

Conflict of Interest: No conflict of interest was declared by the authors.

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

Main Points

- Vocal fold nodules (VFNs) are the common causes of hoarseness in the population.
- There is not enough evidence as to which method is effective in the treatment of patients with VFN.
- There is no research presenting the results of the use of DoctorVox voice therapy (DVT) in the treatment of VFNs.
- In this study, we aimed to evaluate the efficiency of DVT for the treatment of VFNs.
- This study revealed that DVT significantly improved objective and subjective voice-related parameters in patients with VFN. DVT technique can be applied as an effective treatment for VFN.

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Protective and Therapeutic Effect of Platelet-Rich Plasma on Experimental Cisplatin Ototoxicity

Original Investigation

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Abstract

Objective: Cisplatin is a chemotherapeutic agent with an ototoxic effect that is frequently used in head and neck cancers. There are studies in the literature conducted with various antioxidant substances to protect and/or prevent ototoxicity. This study aims to investigate whether platelet-rich plasma (PRP) has a protective and therapeutic effect on cisplatin ototoxicity.

Methods: A total of 40 Sprague Dawley albino rats were divided into six groups as control group (n=6), PRP-only group (n=6), cisplatin group (n=6), cisplatin + PRP group (n=6), PRP + cisplatin group (n=6), and donor group (n=10). At the beginning of the study and the 8th day, they were tested with distortion product otoacoustic emission (DPOAE). Assessment of DPOAE results was based on the signal-to-noise ratio in 2000, 3000, 4000, 6000, and 8000 Hz frequency bands. On the 8th day, the rats were sacrificed. For histological examinations, the temporal bones were dissected and fixed. After hematoxylin and eosin staining, the tissues were evaluated by light microscopy.

Results: In the DPOAE tests performed on the 0th and 8th days of the cisplatin group, it was observed that cisplatin caused hearing loss in the rat ears. It was determined that the cisplatin group at 2000 Hz, 3000 Hz and 4000 Hz had a significant decrease in hearing compared to all groups ($p<0.015$), while the cisplatin group at 6000 and 8000 Hz was characterized by hearing loss at a higher rate than all groups ($p<0.001$). At the end of the study, negative effects of cisplatin on both cellular dimensions (cytoplasmic vacuolization, cell degeneration, dilatation, apoptotic cells, nerve degeneration) and hearing function were observed. No protective or therapeutic effect of PRP on cisplatin ototoxicity was observed.

Conclusion: Our study showed that platelet-rich plasma did not have a significant effect in the treatment of hearing loss due to cisplatin ototoxicity and in preventing hearing loss in rats.

Keywords: Ototoxicity, hearing loss, cisplatin, otoacoustic emissions, platelet-rich plasma, animal experimentation

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Cite this article as: *Gözaydın B, Ünal A, Özdemir D, Çeçen A, Bakırtaş M. Protective and Therapeutic Effect of Platelet-Rich Plasma on Experimental Cisplatin Ototoxicity. Turk Arch Otorhinolaryngol 2023; 61(2): 75-82*

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Received Date: 03.08.2022
Accepted Date: 02.03.2023

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DOI: 10.4274/tao.2023.2022-7-9

Introduction

Ototoxicity refers to the occurrence of the symptoms of hearing loss and/or balance disorder via functional impairment or cellular degeneration in the inner ear caused by exposure to different therapeutic agents and chemicals. There should be the development of sensorineural hearing loss of 20 dB or more in at least two subsequent frequencies so that it is possible to talk about ototoxicity in the audiological evaluation (1-3). Numerous drugs and chemicals such as antibiotics of the aminoglycoside group, many antineoplastic agents including cisplatin, some diuretics, anti-inflammatory and antimalarial drugs and some antiseptic solutions, arsenic, and ethyl and methyl alcohol are known to have ototoxic effects (1, 2).

Cisplatin (cis-diamminedichloroplatinum-II) is a chemotherapeutic agent which is effectively, successfully, and commonly used to treat various malignant diseases such as testicular cancers, head and neck cancers, small cell lung cancer, ovarian cancers, central nervous system malignancies, gastric cancers, and bladder cancers (2, 3). Cisplatin frequently causes ototoxicity and nephrotoxicity and may have significant adverse effects such as bone marrow suppression, gastrointestinal toxicity, and peripheral neuropathy that limit its use in clinical practice (1, 3). In particular, nephrotoxicity and ototoxicity are major dose-limiting adverse effects. These effects are dose-dependent, cumulative and usually lasting. Its nephrotoxic effects can be overcome with hydration; however, there is still no treatment to avoid its ototoxic effects (1-3).

Cisplatin-induced hearing loss is generally progressive, bilateral, symmetrical, irreversible and sensorineural in character. Hearing loss first starts at high frequencies and then gets into lower frequencies over time (4, 5). The ototoxic effects of cisplatin result from the fact that it gradually destroys outer hair cells from the basal to the apical parts of the cochlea. In the literature, several antioxidant substances were used to avoid and/or prevent this ototoxicity (1, 2, 4-7).

Platelet-rich plasma (PRP) was developed as a byproduct of multi-component blood products in the early 1970s. Autologous PRP is the plasma with a high platelet concentration, which is rich in growth factors and obtained from the person's own blood by centrifuging the whole blood. The density and activity of platelets in PRP are four times higher compared to those in whole blood (8). In addition to their role in hemostasis, platelets also play a significant role in the repair of tissues by releasing growth factors from α-granules in tissue damage (9). Alpha granules, platelet-derived growth factor (PDGF), transforming growth factors α and β, epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF) also contain cytokines and chemokines. Growth factors, cytokines, chemokines and other secretory molecules known as integrins are abundant in young platelets and they continue to be secreted in small amounts throughout the 7–10-day life span of the platelets. PDGF increases the number of fibroblasts in the damaged area by stimulating the growth of endothelial cells and ensures the differentiation of neutrophils and monocytes. Thus, capillary vessel formation, increasing collagen production and granulation formation are supported. TGF-β is of vital importance in the restructuring of the skin: for example, in addition to stimulating collagen synthesis during the wound healing process, it also participates in the inflammatory response with PDGF and stimulates the synthesis of extracellular matrix. EGF takes part in chemotaxis and stimulates the proliferation of keratinocytes and fibroblasts. Proliferating fibroblasts increase collagen production. VEGF stimulates the proliferation of endothelial cells, thereby increasing new vessel formation, increasing existing capillary permeability, and contributing to the microenvironment necessary for cell growth and angiogenesis (8, 9).

While PRP is known to be used especially in orthopedics, periodontology, facial plastic surgery, chest and cardiovascular surgery and ophthalmology because of its positive effects on healing, its use in novel indications in ear, nose, and throat practice has drawn attention in recent years (8-11).

This study aimed to investigate the efficacy of PRP in the prevention and treatment of oxidative damage in experimentally induced cisplatin ototoxicity in rats.

Methods

This study was approved by the Experimental Animals Ethics Committee of Recep Tayyip Erdoğan University, Rize, Turkey (decision no: 2017/13, date: 29.03.2017). A total of 40 male adult (3–5 months old) Sprague-Dawley albino rats weighing 250–350 g were used in this study. The principles of the Declaration of Helsinki were followed for all procedures. The study was carried out in the animal experiments laboratory of the university.

All animals were cared for and fed in a sterile experimental animal unit environment with 12-hour light and 12-hour dark cycle at a moisture of 55–60% and at a room temperature of 22°. The external auditory canals and middle ears of the rats were examined by otoscopic examination. By cleaning the plugged ears, the rats with infection in the external auditory canal, opacification and perforation of the tympanic membrane and infection in the middle ear were excluded from the study and new rats were included in the study for completing the number of groups. The rats that died during follow-up and developed otitis were excluded from the study and new rats were included in the study. Before starting the study, distortion product otoacoustic emission (DPOAE) was performed on the rats in all groups and baseline signal-to-noise ratio (SNR) values at each frequency were calculated. SNR values were calculated by performing

DPOAE again on the 8th day of the study. Obtained SNR values were compared within and between groups. Since no significant difference was found between the two ears in the in-group evaluations, the measurements were evaluated on the right ear.

Platelet-Rich Plasma and Its Preparation

The rats from group 6, which were reserved as PRP donors for the intratympanic administration of PRP on days 1, 3, 5, and 7, were sacrificed and intracardiac blood was collected. Approximately 10 mL of blood taken for the intratympanic administration of PRP was added to anticoagulant tubes containing acid citrate dextrose for the preparation of PRP and shaken for 10 seconds to ensure mixing. When it was centrifuged at a low speed (3000 rpm, three minutes), three parts were differentiated in the tube. While erythrocytes were present in the lower part, a platelet-leukocyte mixture called buffy coat was present in the middle part and plasma was present at the top. When the buffy coat and the platelet-poor plasma at the top were recentrifuged at 4000 rpm for three minutes, PRP at a concentration of 10% was obtained.

Control and Experimental Groups

After adequate time passed for adaptation to laboratory conditions, 40 experimental animals were randomly allocated into six groups, six rats in each group and 10 rats in the donor group.

The rats were anesthetized, then distortion product otoacoustic emission (DPOAE) recordings were performed, and their hearing thresholds were identified. The evaluation of DPOAE results was based on the SNR in 2000, 3000, 4000, 6000, and 8000 Hz frequency bands. The SNR is more reliable for the evaluation of DPOAE responses than DPOAE amplitudes.

Group 1 (control group/n=6) was defined as the control group. No injection was administered to this group. DPOAE recordings were taken at the beginning of the study and on day 8.

Group 2 (PRP control group/n=6) was administered PRP (0.1–0.3 mL) intratympanically for four days every other day. DPOAE recordings were taken at the beginning of the study and on day 8.

Group 3 (cisplatin group/n=6) was defined as the cisplatin control group. This group was administered 16 mg/kg single dose cisplatin (cisplatin DBL 100 mg/100 mL vial, Orna İlaç, İstanbul, Turkey) intraperitoneally. DPOAE recordings were taken at the beginning of the study and on day 8.

Group 4 (cisplatin + PRP group/n=6) was intraperitoneally administered 16 mg/kg single dose cisplatin (cisplatin DBL 100 mg/100 mL vial, Orna İlaç, İstanbul, Turkey). Then, PRP (0.1–0.3 mL) was administered intratympanically every other day on days 1, 3, 5, and 7; four doses in total. DPOAE recordings were taken at the beginning of the study and on day 8. The therapeutic effect of PRP on ototoxicity was evaluated.

Group 5 (PRP + cisplatin group/n=6) was administered PRP (0.1–0.3 mL) intratympanically every other day on days 1, 3, 5 and 7; four doses in total. 16 mg/kg single dose cisplatin (cisplatin DBL 100 mg/100 mL vial, Orna İlaç, İstanbul, Turkey) was intraperitoneally administered on day 3. DPOAE recordings were taken at the beginning of the study and on day 8. The protective effect of PRP on ototoxicity was evaluated.

Group 6 (PRP donor group/n=10) was defined as the group to be used as a donor group for the supply of PRP.

Auditory Assessment

DPOAEs were measured in the DPOAE mode using an Echoport ILO292-II (Otodynamics, Hatfield, UK) device. The rat's head was placed in a horizontal position in a quiet room and then the measurement was performed using the neonatal probe suitable for the external auditory canal. The measurement was initiated after seeing that the device was in an appropriate measuring position with a suitable configuration of the probe indicator and stimulus waveform on the device. DPOAEs were measured with a microphone in the external auditory canal and recorded at frequencies of 2000, 3000, 4000, 6000 and 8000 Hz. The values of DPOAE amplitudes that were 3 dB above the noise threshold were considered significant. The evaluation of DPOAE results was based on the SNR that occurred in 2000, 3000, 4000, 6000 and 8000 Hz frequency bands. The SNR is more reliable for the evaluation of DPOAE responses than DPOAE amplitudes. The SNRs were evaluated specifically to frequency for each rat in our study. SNR frequency curves were drawn. All subjects underwent DPOAE testing at the beginning of the study and the baseline values were calculated. DPOAE measurements were performed again eight days after the administration of cisplatin.

Histopathological Evaluation

After the final DPOAE test was performed, all rats were sacrificed for the histopathological evaluation of our study. The bulla was opened after dissecting the temporal bones. After removing the lateral wall of the cochlea and slowly injecting the 2.5% solution of glutaraldehyde, fixation was performed. The temporal bones were kept in the same solution at +4 °C overnight. After fixation, the temporal bones were kept in a 10% solution of EDTA at +4 °C for 10 days for decalcification. The cochlea specimens were dehydrated with ethanol and then embedded in paraffin blocks. The paraffin blocks were prepared in 5-micron-thick sections and then stained with hematoxylin and eosin (H&E). At least 15 sections were evaluated for

each rat cochlea. In the histopathological evaluation, cell degeneration was evaluated using a light microscope by performing a blind rating between 0–4 based on the area of degeneration at x100 magnification as 0: normal (no degenerate cells), 1: mild (1–5 cells degenerate), 2: medium (5–10 cells degenerate), 3: intermediate-advanced (10–15 cells degenerate), 4: advanced degree (15 or more cells degenerated). The median values of the histopathological blind grading of cytoplasmic vacuolization, dilatation, apoptotic cells and nerve degenerations in the groups are summarized in Table 1.

Statistical Analysis

The variables measured by the DPOAE test and histopathological variables of the subjects in the six groups were compared both within and between the groups. The median value was used because the distribution of the data did not fit the normal distribution. All statistical comparisons were performed in a computer environment using the SPSS 16.0 package program (Chicago, IL, USA). In intra- and inter-group comparisons, the t-test and the Mann-Whitney U test were used for normally distributed data and non-normally distributed data, respectively. In all measurements, a p-value <0.05 was considered significant.

Results

Regarding the DPOAE results, DPOAE was performed on rats in all groups before starting the study and then the baseline SNR values at each frequency were calculated (first measurement). On day 8 of the study, the SNR values were calculated by once more performing the DPOAE (last measurement). The SNR values obtained were compared within and between the groups. The measurements were evaluated over the right ear since there was no significant difference between the two ears in the evaluations made within the groups. The SNR values at 2000, 3000, 4000, 6000 and 8000 Hz were compared between the groups before and after the study. It was observed that there were no significant differences between the groups before the procedure (p>0.05) (respectively; p=0.722, p=0.195, p=0.224, p=0.676, p=0.321).

No significant differences were identified in terms of hearing in the DPOAE tests of the group 1 performed on days 0 and 8 (p>0.05) (respectively; p=0.523, p=0.082, p=0.112, p=0.486, p=0.735) (Figure 1, Chart 1).

No significant differences were observed in terms of hearing in the DPOAE tests of the group 2 performed on days 0 and 8 (p>0.05) (respectively; p=0.292, p=0.782, p=0.248, p=0.116, p=0.935) (Figure 1, Chart 2). The PRP extract was found to have no effect on hearing in the normal ear.

In the DPOAE tests of the group 3 performed on days 0 and 8, it was observed that cisplatin caused a significant hearing loss at all frequencies (2000 Hz; p=0.013, 3000 Hz; p=0.003, 4000 Hz; p=0.001), which was more significant at 6000 and 8000 Hz (p<0.001), compared to the other groups (Figure 1, Chart 3).

There was a significant difference in terms of hearing in the DPOAE tests of the group 4 performed on days 0 and 8 (p<0.05) (2000 Hz; p=0.011, 3000 Hz; p=0.003, 4000 Hz; p=0.001, 6000 Hz; p<0.001, 8000 Hz; p<0.001). It was found that the hearing loss caused by cisplatin in the rats' ears was not treatable with PRP plasma (Figure 1, Chart 4).

There was a significant difference in terms of hearing in the DPOAE tests of the group 5 performed on days 0 and 8 (p<0.05) (2000 Hz; p=0.010, 3000 Hz; p=0.006, 4000 Hz; p=0.001, 6000 Hz; p<0.001, 8000 Hz; p<0.001). It was observed that the hearing loss caused by cisplatin in the rats' ears could not be prevented by PRP (Figure 1, Chart 5).

In the histopathological light microscopic examination group 1 showed that the general structure of the tissue was observed to have a normal histological appearance, group 2 revealed that the tissue had a normal histological structure and that PRP had no positive or negative effect on either the morphology or the cellular structures of the tissues and was observed to have normal histological structures, group 3 it was found that the general structure of the tissue deteriorated, cytoplasmic vacuolization increased in the cells, and degeneration-related cell shedding was observed, it was observed that the general structure of group 4 and group 5 tissue was affected by cisplatin and morphologically deteriorated, cytoplasmic vacuolization and degeneration in

Table 1. Grading of histological parameters in groups

Group	Cytoplasmic vacuolization	Cell degeneration	Dilatation	Apoptotic cells	Nerve degeneration
Control group	0,0,0,0,1,0	0,0,0,0,0,1	0,0,1,0,0,0	0,0,0,1,1,1	0,0,0,0,1,1
PRP control group	0,0,0,0,1,1	0,0,0,0,0,0	0,0,0,1,0,1	0,0,0,1,1,1	0,0,0,0,1,1
Cisplatin group	3,3,4,4,4,4	3,3,3,3,3,4	2,2,3,4,3,3	3,3,3,3,3,3	2,2,2,2,3,3
Cisplatin + PRP group	3,3,3,3,3,3	4,3,4,4,4,4	3,3,3,3,3,3	2,2,3,4,3,3	2,2,2,3,3,3
PRP + cisplatin group	3,3,3,3,3,3	2,2,3,3,3,3	4,3,4,4,4,4	3,3,3,3,3,4	2,2,3,4,3,3

PRP: Platelet-rich plasma

cells were more frequent than in the control group, although there was a minimal difference with the cisplatin group, there was no pathologically significant difference (Figure 2).

There were no statistically significant differences between the control group and the PRP control groups, cisplatin group and the cisplatin + PRP therapeutic and PRP + cisplatin protective groups, PRP control group and the cisplatin + PRP therapeutic and PRP + cisplatin protective groups in terms of all evaluation criteria ($p>0.05$).

There was a statistically significant difference between the control group and the cisplatin group in terms of all evaluation criteria ($p<0.005$) (Table 1).

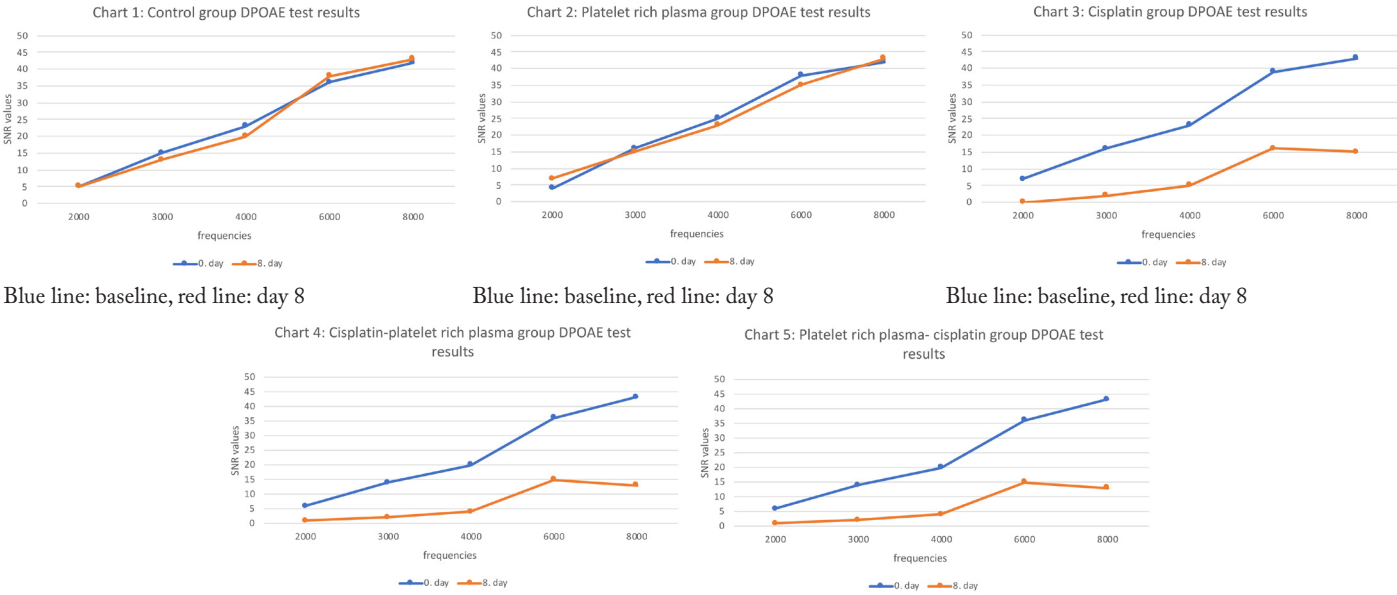

Figure 1. Days 0 and 8 SNR values of the groups at all frequencies

SNR: Signal-to-noise ratio, DPOAE: Distortion product otoacoustic emission

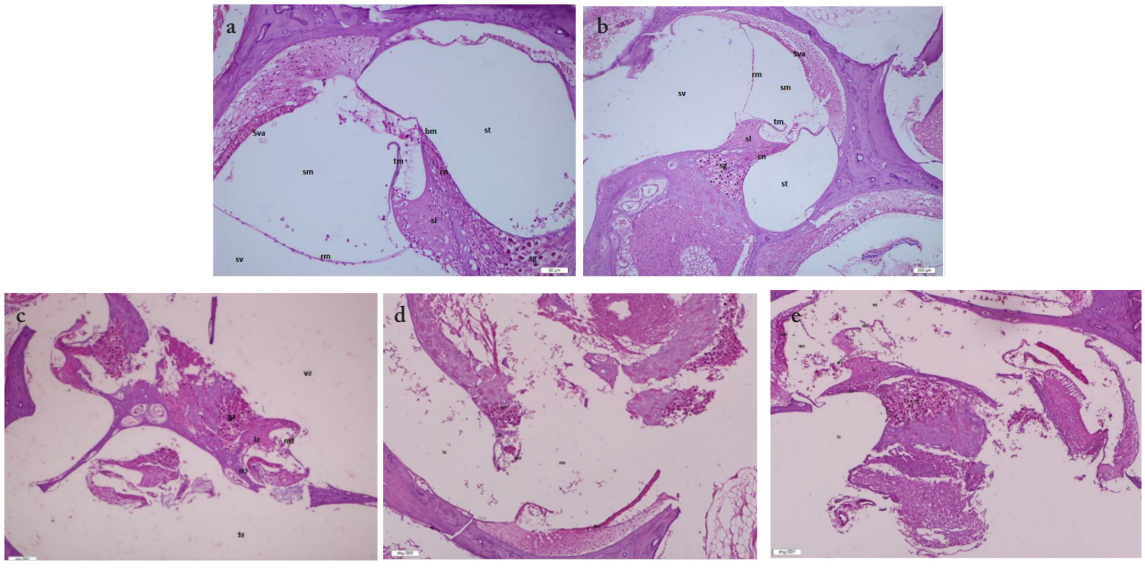

Figure 2. Image of inner ear structures examined with light microscopy in groups. **a)** Control group, normal histological appearance inner ear structures (Hematoxylin and eosin stain, x200). **b)** Platelet-rich plasma group, normal histological appearance inner ear structures (Hematoxylin and eosin stain, x200). **c)** Cisplatin group, increased cytoplasmic vacuolization and degeneration of inner and outer hair cells (Hematoxylin and eosin stain, x40). **d)** Cisplatin + PRP group, cytoplasmic vacuolization and degeneration in cells (Hematoxylin and eosin stain, x40). **e)** PRP + Cisplatin group, cytoplasmic vacuolization and degeneration in cells (Hematoxylin and eosin stain, x40)

SL: Spiral limbus, Rm: Reissner membrane, Sv: Scala vestibuli, Sm: Scala media, St: Scala tympani, bm: Basilar membrane, tm: Tectorial membrane, Cn: Cochlear nerve, Sva: Stria vascularis, Sg: Spiral ganglion and spiral ganglion cells, Sl: Spiral ligament

Discussion

One of the important causes of hearing and balance impairment is ototoxicity. Hearing loss, tinnitus, imbalance and vertigo are the major complaints caused by ototoxic substances. Tinnitus is the most common and often the first symptom among these complaints (12). The route of administration, cumulative dose, age, dietary factors, serum protein levels, genetic factors, use of additional ototoxic drugs, presence of nephropathy, exposure to noise and history of cranial radiotherapy are among the factors that affect the incidence of ototoxicity (3).

Cisplatin-induced ototoxicity is generally manifested with tinnitus starting at high frequencies and hearing loss. However, it ultimately extends to lower frequencies and affects speech perception. These effects are dose-dependent, cumulative and usually lasting. Histopathological examinations revealed that outer hair cells in the basal and middle parts of the cochlea were areas that were mostly affected by cisplatin ototoxicity (2, 4).

The molecular and cellular mechanisms of cisplatin ototoxicity have not been fully understood. Nevertheless, it is known that oxidative stress may be very important for the pathogenesis of ototoxicity. Cisplatin leads to oxidative damage and apoptosis in the cochlea and outer hair cells by increasing the production of free oxygen radicals. Furthermore, it decreases antioxidant enzyme levels through the excessive production of free oxygen radicals. Along with the consumption of antioxidant enzymes, superoxide, hydrogen peroxide and toxic lipids result in the penetration of calcium into cochlear cells by triggering apoptosis (3). In case of the disruption of stability between the production of free oxygen radicals and the antioxidant defense mechanisms, oxidative stress may lead to cochlear cell damage or death (3, 4).

For the prevention of ototoxicity occurring with the use of cisplatin due to the widespread use of this drug as an antineoplastic drug, experimental studies have been conducted with many antioxidant drugs such as ginkgo biloba (gb), sodium thiosulphate, diethyldithiocarbamate, 4-methylthiobenzoic acid, ebselen and lipoic acid, thymol, vitamin E and steroids (1, 2, 4-7).

In their experimental study, Huang et al. (6) evaluated the effects of gb extract, an anthocyanin, on cisplatin ototoxicity through hearing and histopathological examinations. In the study, both a smaller decrease in hearing thresholds and a lower level of outer hair cell destruction were found in the group receiving gb + cisplatin compared to the group receiving only cisplatin and this difference was statistically significant.

Wang et al. (7) administered sodium thiosulphate, whose autoprotective effect has been known for a long time, during the administration of cisplatin in rats, in the form of intracochlear perfusion at a clinically high therapeutic dose. This strategy was highly successful and it was reported that no signs of hearing loss were observed. In histological analyses, nearly full protection of outer hair cells was observed in the organ of Corti; however, there was a significant loss in hearing and outer hair cells in the cisplatin-treated group.

Rybak (13) found that the use of antioxidants or preservatives such as diethyldithiocarbamate, 4-methylthiobenzoic acid, ebselen, and lipoic acid protected the cochlea against cisplatin damage and prevented hearing loss.

Koçak et al. (5) suggested that thymol, a natural monoterpene phenolic compound, could prevent cisplatin ototoxicity by increasing the antioxidant enzymes and reducing oxidant parameters. Until today, no agent has been widely accepted for use in clinical practice. Thus, alternative effective and protective treatments are still being investigated. In the presented study, we aimed to evaluate audiologically and histopathologically the protective and therapeutic effects of PRP on cisplatin ototoxicity in rats, as it is being used in many areas, especially in recent years, for its antioxidant activity in the prevention of cisplatin ototoxicity. PRP is obtained from autologous whole blood and has crucial roles in bone and soft tissue healing since it includes a high concentration of growth factors and cytokines.

In the literature, there is one study in which Yurtsever et al. (2) investigated whether PRP provided protection against cisplatin ototoxicity. In their study, they compared the study group, in which cisplatin was administered and PRP was used for preventive effect, with the control group, which received intratympanic saline and demonstrated that the number of outer hair cells in the organ of Corti decreased significantly in the PRP-treated group compared to the control group. They reported that PRP could prevent cisplatin-induced ototoxicity. The researchers indicated that the small number of animals used and the fact that the study was conducted with light microscopy were the weaknesses of the study. Compared to our study, it was considered that the difference between the results could be due to the small number of animals used, differences in forming the groups, and the evaluation of hearing at different times after PRP.

Terzi et al. (4), examining the efficacy of astaxanthin as a protective agent against cisplatin-induced ototoxicity, concluded that astaxanthin could protect hearing from cisplatin-induced ototoxicity, prevent cellular degeneration and significantly reduce oxidative stress. The authors reported the limitation of the study as the lack of DPOAE measurement at frequencies higher than 8 kHz, the H&E staining of the cochlea only, and the lack of immunohistochemistry staining to show apoptosis.

Among the studies in the literature conducted in the field of otolaryngology, there are various studies demonstrating the positive effects of PRP on tissue regeneration in tympanic membrane perforations, after rhinoplasty operations, after septoplasty and endoscopic sinus surgery by being absorbed into nasal packings, in vocal cord injuries and acute facial nerve injuries (14-18).

In the data we obtained at the end of the study, it could not be determined by DPOAE that PRP had a protective or therapeutic effect against hearing loss due to cisplatin ototoxicity at frequencies of 2000 Hz and above. In the histopathological evaluation, cisplatin's ototoxic effects were observed at the cellular level and no significant difference was found in terms of the protective or therapeutic efficacy of PRP. No significant antioxidant activity of PRP against cisplatin-induced ototoxicity was found in histopathological evaluation.

According to the histological results of our study, no statistical significance was observed in terms of the cytoplasmic vacuole, cell degeneration and dilatation, nerve degeneration and apoptosis when the cisplatin group and cisplatin + PRP groups were compared.

In the literature, there are various studies on tissue regeneration of PRP; however, limited studies on its effect on ototoxicity are available. As a result of otoacoustic emission and histopathological examinations in our study, it was observed that PRP did not have a significant effect on the protection of hearing and treatment of hearing loss in cisplatin ototoxicity.

Conclusion

For many years, numerous studies have been conducted to find ways to protect against cisplatin ototoxicity. However, no specific agent has been reported that can be transferred to routine clinical practice based on the results obtained from these studies.

We investigated the therapeutic and protective efficacy of PRP against cisplatin ototoxicity in our study. Although the therapeutic and protective efficacy of PRP against cisplatin ototoxicity is found in the literature, we could not obtain statistically significant results in our study. Nevertheless, there is a need for further studies to investigate the effects of PRP on different species at different doses with different routes of administration and duration of treatment.

Ethics Committee Approval: This study was approved by the Experimental Animals Ethics Committee of Recep Tayyip Erdoğan University, Rize, Turkey (decision no: 2017/13, date: 29.03.2017).

Informed Consent: The study does not require patient consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.G., A.Ü., D.Ö., Concept: B.G., A.Ü., Design: B.G., A.Ü., Data Collection and/or Processing: B.G., D.Ö., Analysis and/or Interpretation: B.G., A.Ü., D.Ö., M.B., Literature Search: B.G., A.Ç., Writing: B.G., A.Ü., A.Ç.

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

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

Main Points

- Cisplatin-induced ototoxicity is generally manifested with tinnitus starting at high frequencies and hearing loss.
- In the literature, several antioxidant substances were used to avoid and/or prevent this ototoxicity.
- Platelet-rich plasma (PRP) is obtained from autologous whole blood and has crucial roles in bone and soft tissue healing since it includes a high concentration of growth factors and cytokines.
- In the literature reported in the field of otolaryngology, there are various studies demonstrating that PRP has positive effects on tissue regeneration.
- We investigated the therapeutic and protective efficacy of PRP against cisplatin ototoxicity in our study.
- Although the therapeutic and protective efficacy of PRP against cisplatin ototoxicity is found in the literature, we could not obtain statistically significant results in our study.
- Nevertheless, there is a need for further studies to investigate the effects of PRP on different species at different doses with different routes of administration and duration of treatment.

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Thermal Welding Tonsillectomy versus Monopolar Electrocautery Tonsillectomy: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

Systematic Review

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Abstract

Objective: In hopes of contributing to the decision about the best surgical option in tonsillectomy, we performed this work to compare the effectiveness of the thermal welding system (TW) and monopolar electrocautery (ME) tonsillectomy in terms of postoperative pain, postoperative bleeding, and operation time in patients undergoing tonsillectomy, to determine which procedure is most expected to enhance the postoperative quality of life.

Methods: Digital databases, including PubMed, Scopus, Cochrane, Web of Science, and Google Scholar, were systematically screened from inception up to October 2022. The included randomized controlled trials (RCTs) were evaluated for risk of bias via the Cochrane tool (version 2). The outcomes were summarized as risk ratio (RR) or mean difference/standardized mean difference (MD/SMD) with a 95% confidence interval (CI) in a random-effects model.

Results: The three RCTs that met our criteria were included in the study. Overall, 151 patients had been enrolled in these three RCTs, in which 75 and 76 were allocated to the TW and ME groups, respectively. The postoperative pain levels were substantially reduced, favoring the TW arm over the ME arm [n=2 RCTs, SMD=-0.39, 95% CI (-0.67, -0.12), p=0.005]. Also, the analysis revealed a substantial variation between the TW and ME arms in terms of operation time [n=2 RCTs, MD=3.29 minutes, 95% CI (1.42, 5.17), p=0.0006]. However, the analysis revealed no substantial variation between the TW and ME arms in term of postoperative bleeding [n=3 RCTs, RR=0.40, 95% CI (0.06, 2.62), p=0.34].

Conclusion: This meta-analysis revealed that postoperative bleeding for tonsillectomy were similar between the ME and TW techniques. However, TW showed lower postoperative pain levels than ME statistically but without achieving significant clinical advantage.

Keywords: Tonsillectomy, thermal welding, monopolar electrocautery, pain, bleeding

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Cite this article as: *Albazee E, Alshammari B, Alotaibi M, Tripathi KM, Abuawad A. Thermal Welding Tonsillectomy versus Monopolar Electrocautery Tonsillectomy: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. Turk Arch Otorhinolaryngol 2023; 61(2): 83-90*

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Received Date: 28.11.2022
Accepted Date: 01.02.2023

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DOI: 10.4274/tao.2023.2022-11-9

Introduction

In otorhinolaryngology, tonsillectomy is among the most often performed operations (1). Recurrent tonsillar infections and tonsillar hypertrophy are the most prevalent reasons for tonsillectomy procedures because the tonsils act as a septic focus and obstruct the upper airway (2, 3).

In the last decades, with advancements in anesthetic and surgical methods, fatality incidents resulting from tonsillectomy

have declined. But still, tonsillectomy is accompanied by severe complications, including pain, hemorrhage, and dietary restrictions (4, 5). New techniques and tools have been introduced to avoid and reduce these comorbidities and complications. The majority of these techniques, such as cold-steel dissection, monopolar electrocautery (ME), bipolar electrocautery (BE), coblation, laser dissection, and thermal welding system (TW) (6-9), work by applying a variety of energy sources to denature the muscles and tissues and block the blood vessels outside of the typical coagulation pathways (10). These approaches have been examined and contrasted in children, adults, and both; nonetheless, TW and ME are currently the most applied approaches (10, 11).

Undertaking a tonsillectomy with TW is an innovative approach. It depends on using temperature, pressure, and time to seal vessels. It depends on applying heat and pressure to block blood vessels. The instrument has a heat source in one arm powered by a low-voltage current set between 300 and 400 degrees Celsius. This heat source is forced against an opposing arm to generate the ideal pressure for tissue fusing and dividing. Additionally, the fusing and dividing process of the tissues is accompanied by evaporation along the constrained area in touch with the heat source (12). The latest research that evaluated the effectiveness of this novel method discovered that TW caused only minimal tissue damage. These investigations presented TW as a secure approach to tonsillectomy procedures. Additionally, they showed that it shortened the operation duration and provided adequate hemostasis during surgery and tissue dissection (13).

ME is among the new techniques used for tonsillectomy. ME abrades structures and tissues around the tonsils by producing an electric discharge between the tissue and the ME. It sections tissues at 400 ˚C or above. It coagulates vasculature and separates the tissue holding the tonsil to the underneath pharyngeal constrictor muscles by applying high heat to the tonsillar region. Its use is complicated with issues relating to postoperative comorbidities, including thermal damage to adjacent structures. Thermal injury to the pillar mucosal layer might delay healing and aggravate late problems involving postoperative bleeding and pain (14).

Despite the various advantages offered by the current procedures and technologies, there still has to be clarity on the approach and technology that will result in the least amount of postoperative discomfort and the highest level of safety in tonsillectomy (15, 16). In hopes of contributing to the decision about the best surgical option in tonsillectomy, we performed this work to compare the effectiveness and safety of the TW and ME tonsillectomy in terms of postoperative pain, postoperative bleeding, and operation time in patients undergoing for tonsillectomy to determine which procedure is most expected to enhance the postoperative quality of life.

Methods

We adopted the Cochrane Handbook guidelines for Systematic Reviews, besides the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (17, 18). Ethical approval was exempted since this type of a study is based on published articles.

Eligibility Criteria and Study Selection

We included (i) patients: individuals undergoing tonsillectomy; (ii) intervention: thermal welding technique; (iii) comparison: ME technique; (iv) study outcomes: reporting of one of our specific endpoints (operation time, postoperative pain, and postoperative bleeding); and (v) study design: randomized controlled trials (RCTs). The exclusion criteria comprised: (i) procedures other than tonsillectomy; (ii) procedures other than TW and ME, such as conventional dissection, coblation, and laser; and (iii) studies other than RCTs, such as case reports, observational studies, review articles, and letters.

Information Sources, Search Strategy, and Study Selection

Digital databases, including PubMed, Scopus, Cochrane, Web of Science, and Google Scholar, were systematically screened from inception up to October 2022. Our search strategy comprised: (tonsillectom* or adenotonsillectom* or “tonsil surgery” or “tonsil removal” or “tonsillar surgery” or “tonsillar removal”) and (“thermal welding” or thermal or welding or “tissue welding” or “thermal welding system” or “thermal fusion”) and (monopolar or unipolar or electrocautery or “unipolar cauterization” or “monopolar cauterization”). To widen our search for relevant studies, we looked through the references of the eligible trials and the recent reviews. The method for choosing the studies involved excluding duplicate citations, title/abstract screening, and full-text examination of the possible resources. In a separate way, two authors completed the search strategy and selected studies; in case of discrepancies, we contacted and consulted the principal investigator.

Quality Assessment of the Included Studies

The Cochrane risk of bias tool (RoB 2) was used to evaluate the quality of each trial (19). Each assessed domain was given a score for bias risk, which ranged from low to some concerns to high. Two co-authors evaluated the quality of the included studies, and for discrepancies, we adopted consultation with the principal investigator.

Data Collection and Study Endpoints

We collected the baseline summary from the included trials and populations, including the author’s first name and the publication year (study identifier), country, trial duration,

study arms, sample size, type of patients (adult or pediatric), age, gender, and duration of follow-up. Our endpoints included operation time (minutes), postoperative pain score, and postoperative hemorrhage (%). Postoperative pain score was assessed by a 10-point scale (0= no pain, 10= intolerable pain). Furthermore, postoperative bleeding was characterized as primary (in <24 hours) or secondary (in >24 hours). Two co-authors independently collected the data using a predesigned extraction sheet, and discrepancies were settled by consultation with the principal investigator.

Statistical Analysis

The Mantel-Haenszel technique was used to conduct the analyses on dichotomous data, which were pooled as a risk ratio (RR) with a 95% confidence interval (CI). The studies were carried out using the Inverse-Variance method, and continuous data were gathered as mean difference (MD) or standardized mean difference (SMD) with 95% CI. In every analysis, the random-effects model was applied. For heterogeneity, we adopted the chi-square ($p<0.1$ and I-square >50%) and I-square tests (20). We assessed postoperative pain on days 1, 5, and 10. Concerning postoperative bleeding, we clarified it to primary (in <24 hours) and secondary (in >24 hours). For all endpoints, statistical significance was determined as $p<0.05$. The RevMan software (version 5.4 for Windows) was adopted for statistical analysis. Also, subgroup analysis was performed according to the age group (pediatric and adult).

Results

Summary of the Literature Search

From the literature search, we obtained 393 studies, of which 163 were duplicated studies. Of the remaining 230 citations, 223 studies were omitted during title/abstract screening, and the remaining seven studies continued to full-text screening. Finally, three RCTs were included in our pooled analysis (21-23). Figure 1 summarizes the PRISMA flowchart.

Summary of the Characteristics of the Included Studies and the Participants

Overall, 151 patients were enrolled in these three RCTs, in which 75 and 76 participants were enrolled in the TW and ME arms, respectively. These RCTs were conducted in Turkey, the USA, and Finland. Follow-up duration ranged from ten to 30 days. Table 1 summarizes the baseline demographics of the included RCTs and populations.

Summary of the Quality Assessment

The overall quality assessment was a low risk of bias in one RCT and some concerns of bias in one RCT, and a high risk of bias in one RCT (21-23). One RCT was evaluated as having some concerns of bias for the randomization process domain, as no information was provided about the randomization process and the allocation concealment

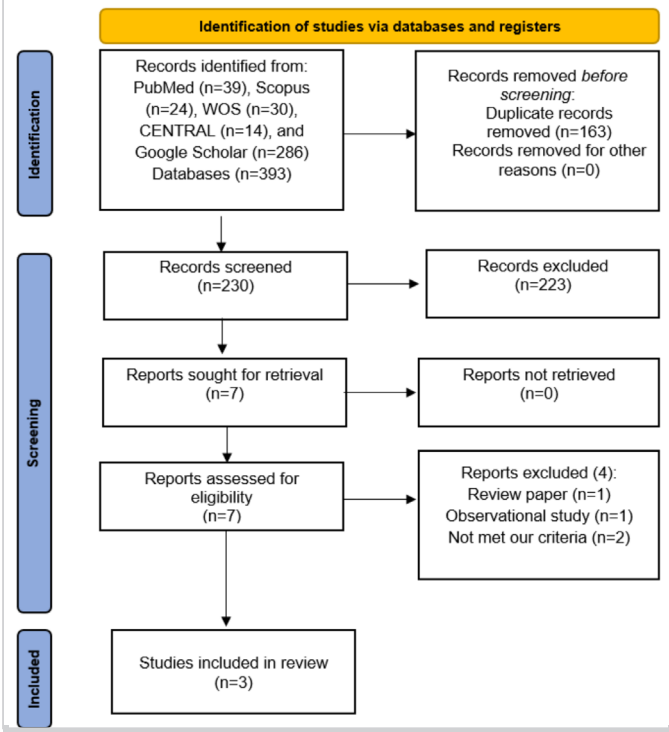

Figure 1. PRISMA flow chart for literature search and study selection

Table 1. Summary of baseline characteristics of the included trials

Study ID	Country	Trial duration	Age group	Trial group	Participants	Age (years) Mean ± SD	Sex, n		Duration of follow-up
							Male	Female	
Cunningham and Chio (21) 2015	USA	N/A	Adults	TW	n=24	18-50 (range)	N/A	N/A	21-30 days
				ME	n=24	18-50 (range)	N/A	N/A	
Dal et al. (22) 2021	Turkey	From December 2017 to December 2018	Pediatrics	TW	n=20	5.3	9	11	10 days
				ME	n=23	5.65	10	13	
Silvola et al. (23) 2011	Finland	N/A	Adults	TW	n=31	26 ±8	14	17	14 days
				ME	n=29	28 ±11	12	17	

N/A: Not available, TW: Thermal welding system, ME: Monopolar electrocautery, SD: Standard deviation

method. For the domain of missing outcome data, one RCT was evaluated as having a high risk of bias due to a lack of detailed information about an important outcome, postoperative pain. Additionally, for the domain of the selection of reported results, one RCT was evaluated as having some concerns of bias because there was a lack of evidence to rule out the potential that reported outcome data were chosen from a variety of outcome measurements. Figures 2 and 3 show the RoB graph and summary, respectively.

Meta-Analysis of the Endpoints

A. Operation duration (minutes)

There was a substantial variation between the TW and ME arms regarding mean operation time [n=2 RCTs, MD =3.29 minutes, 95% CI (1.42, 5.17), p=0.0006]. The gathered analyses were heterogeneous (chi-square p<0.1, I-square >50%) (Figure 4).

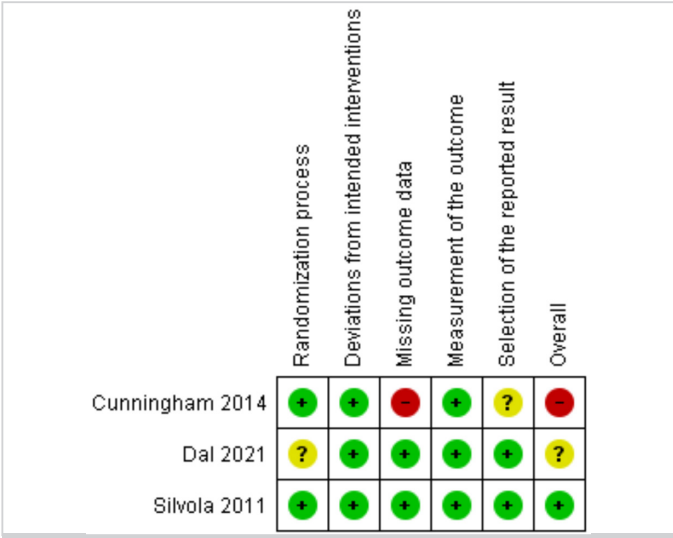

Figure 2. Risk of bias (RoB) graph

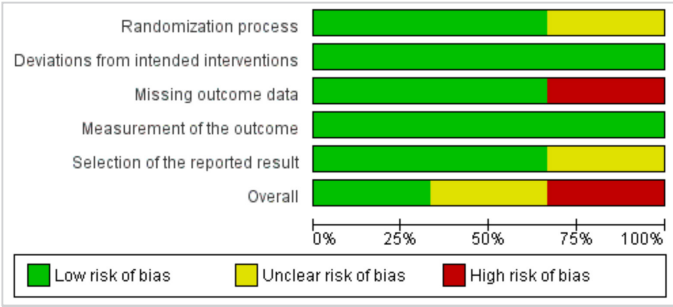

Figure 3. Risk of bias (RoB) summary

B. Postoperative pain (10-point scale)

Postoperative pain levels were substantially reduced in favor of the TW arm compared to the ME arm [n=2 RCTs, SMD =-0.39, 95% CI (-0.67, -0.12), p=0.005]. In subgroup analysis, the effect size was not statistically significant on postoperative day 1 [n=2 RCTs, SMD =-0.36, 95% CI (-0.75, 0.03), p=0.07], however; on postoperative pain day 5 there were a substantially reduction that favor TW arm compared to the ME arm [n=2 RCTs, SMD=-0.43, 95% CI (-0.83, -0.04), p=0.03]. The gathered analyses were homogenous (chi-square p>0.1, I-square <50%) (Figure 5).

In the subgroup analysis by age groups, on day 1 there were no substantial differences between the TW and ME arms in the adults subgroup [n=1 RCTs, MD=-0.41, 95% CI (-0.93, 0.11), p=0.12], and there were no substantial differences between the TW and ME arms in the pediatric subgroup [n=1 RCT, MD =-0.29, 95% CI (-0.89, 0.32), p=0.35] (Supplemental Figure 1). Similarly, on day 5, there was a substantial difference between the TW and ME arms in the adult [n=1 RCTs, MD =-0.58, 95% CI (-1.11, -0.06), p=0.03], and there were no substantial differences between the TW and ME arms in the adult [n=1 RCT, MD=-0.23, 95% CI (-0.83, 0.37), p=0.46], respectively, (Supplemental Figure 2).

C. Postoperative bleeding

Overall, there was no substantial variation between the TW and ME arms regarding postoperative bleeding [n=3 RCTs, RR =0.40, 95% CI (0.06, 2.62), p=0.34]. Subgroup analysis revealed no substantial variation between the two arms regarding the rates of primary bleeding [n=3 RCTs, RR =3.00, 95% CI (0.13, 70.16), p=0.49], and secondary bleeding [n=3 RCTs, RR =0.16, 95% CI (0.02, 1.29), p=0.09]. The gathered analyses were homogenous (chi-square p>0.1, I-square <50%) (Figure 6).

Discussion

This pooled analysis revealed that postoperative bleeding for tonsillectomy were similar between the ME and TW techniques. TW showed lower postoperative pain levels than

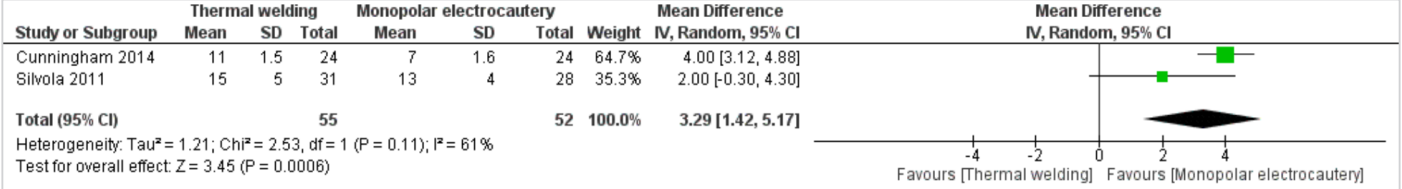

Figure 4. Meta-analysis of the mean the operation duration (min)
SD: Standard deviation, CI: Confidence interval

ME statistically but without achieving significant clinical advantage. Also, ME showed lower operative duration than TW statistically but without achieving significant clinical advantage. Since TW is more costly than ME and the utilization of the TW did not provide any apparent benefits over ME in tonsillectomy, we suggest that the cost factor should be considered when choosing one of these two procedures (21-23).

ME and TW both have the drawback of applying high heat, which might harm the adjacent mucosa and the muscle tissue, and lead to pharynx spasms (22). However, TW contains an insulating component to minimize tissue injury when utilizing this technique (16). This may result in reduced tissue injury to the pharynx muscles, pharynx spasms, as well as postoperative pain. These results aligned with our study, as the TW technique reduced postoperative pain more than ME. Comparing TW to other hot-tonsillectomy methods, Sanlı et al. (16) also concluded it to be a reliable approach in terms of tissue injury.

Comparing the TW and BE procedures, Karatzias et al. (12) discovered that the TW group experienced substantially less pain and no thermal harm to the nearby structures. In the BE arm, they also found a small amount of peritonsillar and uvula edema. Yet, according to Cunningham and Chio (21), there was no substantial statistical variation in pain levels between electrocautery and TW.

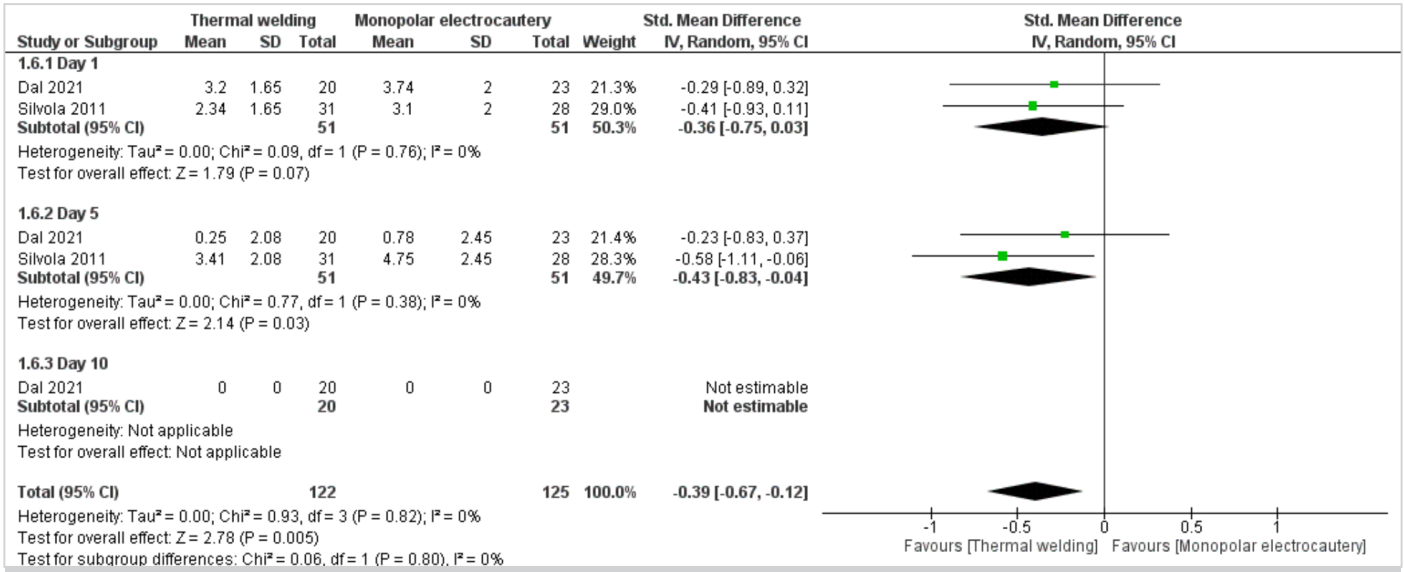

Figure 5. Meta-analysis of the mean postoperative pain (10-point scale)

SD: Standard deviation, CI: Confidence interval

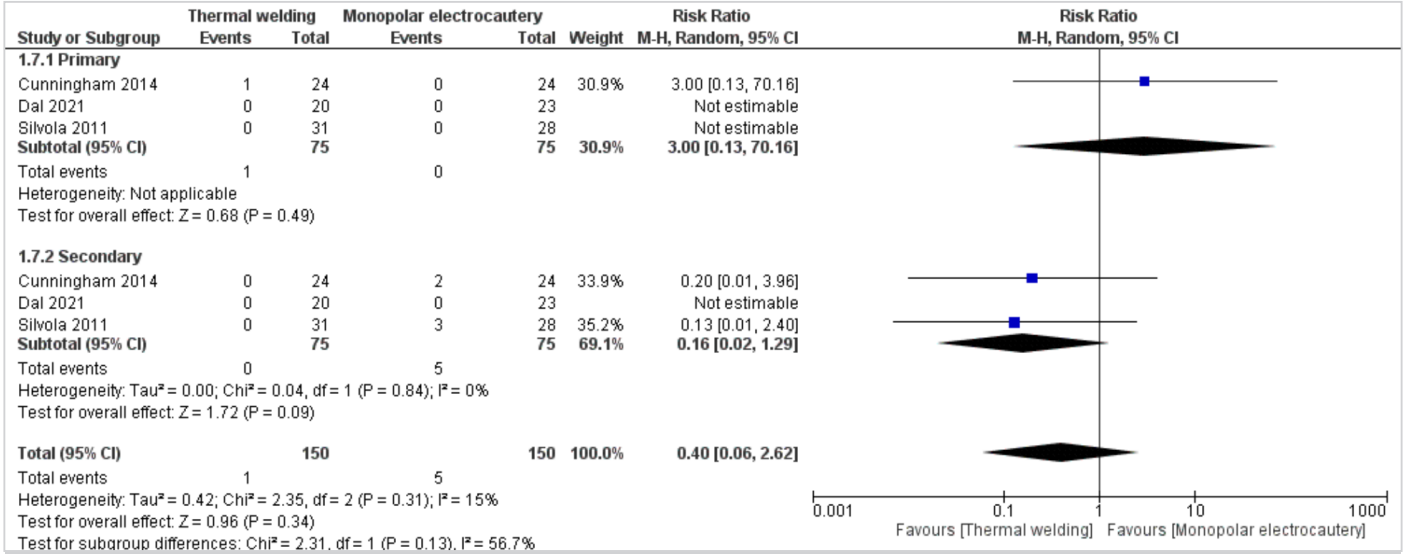

Figure 6. Meta-analysis of the rate of postoperative bleeding

SD: Standard deviation, CI: Confidence interval

A previous investigation on tonsil bed healing and the extent of the necrosis showed that the TW group performed substantially better than the ME group (21). These findings are consistent with those of Ozkiriş et al. (24) who found that the TW group had greater re-epithelization of the tonsillar fossae than the BE dissection approach provided. The amount of thermal tissue injury and pain levels were connected and found to be considerably lower in the TW group. Consequently, analysis of the thermal tissue injury can provide insight into the likely level of postoperative pain that patients will experience after any tonsillectomy approach and affects when patients are discharged from the hospital and how much the procedure costs overall.

Concerning postoperative bleeding, our gathered analysis revealed no substantial variation between the ME and TW techniques in tonsillectomy. According to Hinton-Bayre et al. (25), who reviewed the methods employed by consulting surgeons, there was no substantial variation in secondary post-tonsillectomy bleeding between the trial arms. Additionally, the authors highlighted that as a contributing factor to bleeding, surgeon experience was possibly more crucial than the technology of the tools utilized in these surgeries. According to a prior trial, however, the TW technique could cause fewer bleeding concerns than conventional tonsillectomy techniques (23). In this study, the authors demonstrated that whereas there were no cases of hemorrhage in the TW arm, three individuals in the ME arm experienced late hemorrhage. The small sample size still restricts the results of this study, and large-scale confirming RCTs are required to verify the safety of TW.

TW had the greatest rate of return to the operating room for the management of secondary hemorrhage and the greatest degrees of pain. Whereas the observed extent of the injury was less severe than that of coblation, this result could be due to the high operating temperatures for TW (10). However, when comparing coblation with the laser technique, a recent pooled analysis revealed no substantial variation between the coblation and the laser procedures in terms of postoperative pain and bleeding (26).

Regarding the duration of the operations, we found a significant difference between the TW and ME techniques (21-23). Another trial also found that using TW resulted in prolonged operating times ($p<0.001$). When total anesthetic times were compared, however, this did not result in a statistically significant extension of intraoperative time, and hence, did not result in an increase in cost (21).

Although the majority of otorhinolaryngologists are aware that several modern devices used in tonsillectomy -those used for coblation and TW, for instance- are substantially more costly than those used for ME, the increased operating time had the highest impact on cost (21-23). Another study, supporting these findings, reported a significant increase in operation times and costs in TW compared to ME (21). Yet, there is a lack in the literature concerning the cost of these new techniques. Even the few studies that discussed the cost need to be updated, as they were conducted more than 10 years ago. For example, in 2003, TW forceps cost was estimated to be approximately €280/US$340. These forceps were single-use Bayonet UltraSlim instruments (27). This finding was cost-effective in some investigations as the single-use protects against Creutzfeldt–Jakob disease transmission (12). However, a study conducted in the Turkish population in 2013 reported that the main disadvantage of TW was the cost of the procedure, which was significantly higher than those of BE and classic dissection techniques, as the cost of TW forceps was about US$310 at that time in Turkey (24).

The results of this pooled analysis provide new information. However, some of its drawbacks necessitate caution when generalizing its findings. The inability to assess publication bias and the short postoperative follow-up times are two of these drawbacks. The low number of eligible studies mainly contributed to these limitations. The included studies also revealed a discrepancy in demographic traits depending on whether the group was made up of adults or children, which could introduce bias. Histopathologic characterization of the extent of injury of TW was lacking, and further research involving a larger patient group is required to thoroughly explore the substantial variations between TW and ME.

Conclusion

This pooled analysis revealed that postoperative bleeding for tonsillectomy were similar between the ME and TW techniques. TW showed lower postoperative pain levels than ME statistically, but without achieving significant clinical advantage. Also, ME showed lower operative duration than TW statistically but without achieving significant clinical advantage. Since the TW technique is costlier than the ME and the utilization of TW did not provide any apparent benefits over ME in tonsillectomy, we suggest that the cost factor should be considered when choosing one of these two procedures. Additional well-designed RCTs with greater sample sizes are needed to fully understand and comparatively assess the morbidity rates associated with ME and TW in tonsillectomy.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.A., B.A., Design: E.A., B.A., M.A., K.M.T., A.A., Data Collection and/or Processing: B.A., M.A., K.M.T., A.A., Analysis and/or Interpretation: E.A., M.A., K.M.T., Literature Search: B.A., M.A., A.A., Writing: E.A., B.A., M.A., K.M.T., A.A.

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

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

Main Points

- New techniques have been introduced to avoid comorbidities of tonsillectomy, such as monopolar electrocautery (ME) and thermal welding system (TW).
- Thermal welding may be related to less postoperative pain compared to ME, but this is still without significant clinical advantage.
- Since the surgical outcomes of TW and ME are similar in tonsillectomy, the cost factor may favor ME over TW.

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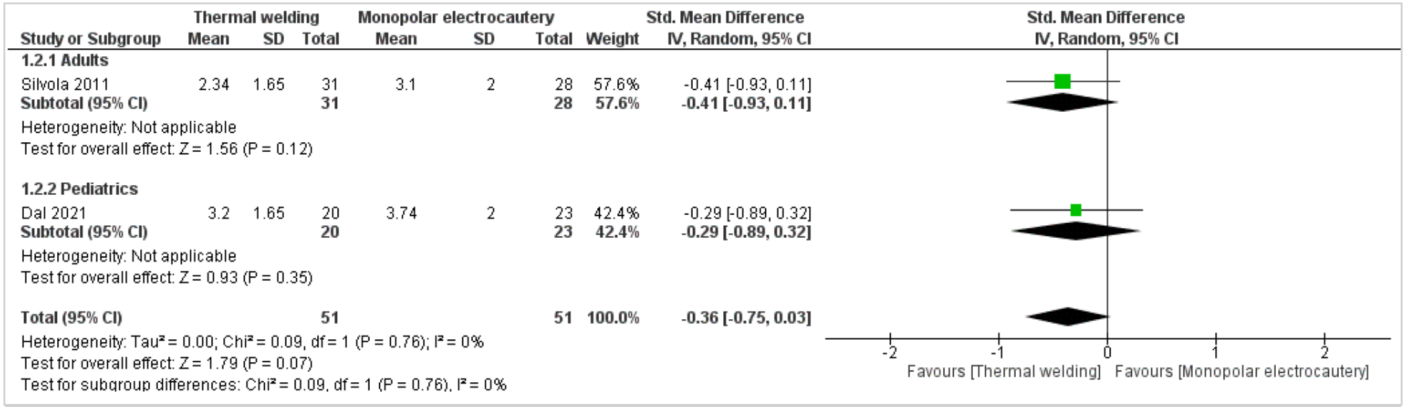
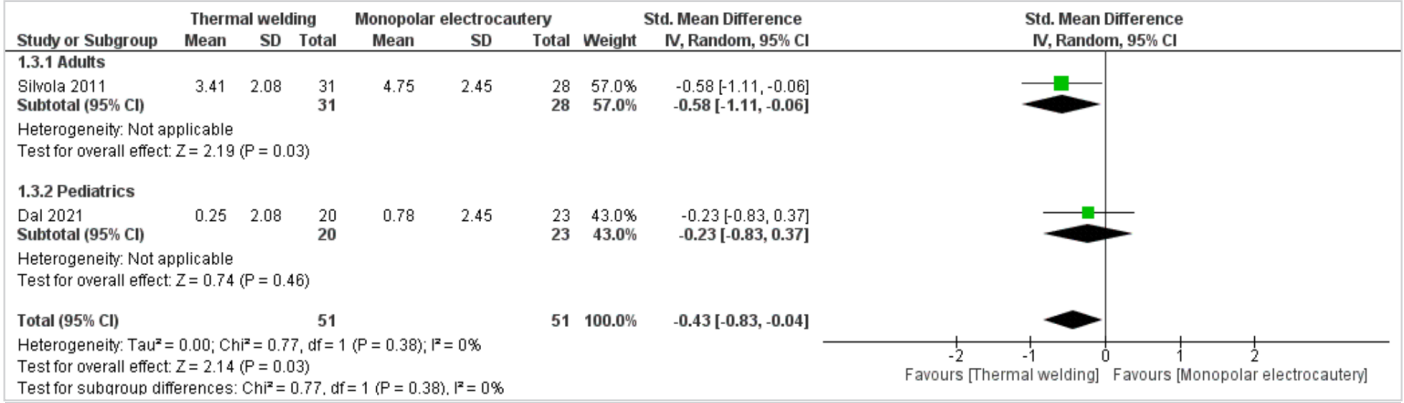


Supplemental Figure 1. Meta-analysis of the mean postoperative pain (day 1)

SD: Standard deviation, CI: Confidence interval



Supplemental Figure 2. Meta-analysis of the mean postoperative pain (day 5)

SD: Standard deviation, CI: Confidence interval

Infratemporal Fossa Abscess Drainage via a Trans-Oral Image Guided Approach

Case Report

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Abstract

Deep neck space infections can cause antibiotic-resistant abscesses that can impinge on vital anatomical structures. Image-guided surgery systems using preoperative computed tomography (CT) imaging can be utilized to characterize pathology and assist surgeons in avoiding iatrogenic injury. This manuscript explores the presentation and unique CT-guided surgical management of an infratemporal fossa abscess in a 48-year-old male who presented with left-sided dental pain and facial swelling that had progressed despite antibiotics and dental extraction. CT-guided imaging can assist in localizing and protecting vital anatomical structures during deep neck abscess drainage and can prevent the potential risks and complications of classic surgical approaches.

Keywords: Deep neck abscess, head and neck surgery, image-guided surgery systems, infratemporal fossa, case report

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Cite this article as: *Morin A, Urban MJ, Al-Khudari S. Infratemporal Fossa Abscess Drainage via a Trans-Oral Image Guided Approach. Turk Arch Otorhinolaryngol 2023; 61(2): 91-94*

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Received Date: 02.02.2023
Accepted Date: 21.05.2023

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DOI: 10.4274/tao.2023.2022-10-10

Introduction

Deep neck space infections (DNSI) may result in severe complications including mediastinitis, airway obstruction, respiratory distress syndrome, aspiration pneumonia, septic shock, disseminated intravascular coagulation, or death (1, 2). DNSI can have major consequences on the integrity of critical anatomical landmarks within the surrounding vicinity. Surgical intervention is indicated for abscesses that fail to respond to antibiotics; however, special care and delicate surgical maneuvers are required to preserve anatomical structures that are not clearly distinguishable. Image-guided surgery systems using preoperative computed tomography (CT) imaging have increasingly been utilized to characterize pathology and assist surgeons in avoiding iatrogenic injury (3, 4). For example, CT imaging has aided in the diagnosis of retropharyngeal abscesses and the indication for surgical drainage in children based on a series of 18 cases (5). CT-guided imaging has long been established for diagnosing various pathologies; however, it has only recently become utilized intraoperatively, especially in our case for guidance in deep neck abscess drainage. While much of the literature on CT-guided surgery in otolaryngology focuses on endoscopic and transnasal approaches, our manuscript reports a unique, image-guided intraoral drainage of an infratemporal fossa (ITF) abscess (6). The primary objective of this work is to report on the minimally invasive approach and review the role of image-guided surgery in the management of DNSI.

Case Presentation

The patient is a 48-year-old male who had no significant medical history and presented

with three weeks of left-sided dental pain and facial swelling that had progressed despite oral antibiotics, intravenous antibiotics, and dental extraction. Physical examination revealed tender edema of the left buccal space extending high over the lateral temporal region, significant trismus, and minimal purulent drainage descending across the left oral vestibular fornix. CT imaging demonstrated a 1.2-cm abscess ascending along the lingual cortex of the left ramus with a separate 2.1-cm abscess in the left ITF and surrounding inflammatory changes (Figures 1a, b). Needle aspiration of both sites (intraoral and transtemporal, respectively) appeared to resolve the abscess along the mandible, but the patient's temporal pain, trismus, and leukocytosis persisted. The decision was then made to proceed with operative drainage of the infection under anesthesia. The patient was hemodynamically stable, informed consent was obtained, and the team proceeded to the operating suite for a left ITF abscess incision and drainage with intraoperative CT image guidance.

The patient was prepped and draped in the usual sterile fashion after nasal fiberoptic intubation with maxillofacial CT image registration (Medtronic Fusion System, Minneapolis, Minnesota, United States). The intraoral approach was initiated via a horizontal mucoperiosteal incision 5 mm above the mucogingival junction over the left maxilla. Subperiosteal dissection proceeded posteriorly towards the pterygomaxillary fissure. At this time, visualization was limited, and blind dissection was halted to avoid neurovascular injury. The image-guided Frazier tip suction and probe were bluntly directed toward the ITF abscess under live image localization and confirmed in 3-dimensions (Figure 2). A rush of purulent exudate was released via blunt dissection with the seeker probe and cultures were sent for examination. The area was irrigated copiously, ½-inch iodoform packing was placed in the abscess cavity, confirmed by image guidance, and the anterior 75% of the mucoperiosteal incision was closed with a dissolvable suture. Empiric antibiotics (vancomycin/piperacillin-tazobactam) were continued. All cultures resulted in no bacterial growth. The patient's symptoms and laboratory findings improved throughout the hospital course, and the patient was discharged on postoperative day three. The CT performed one month postoperatively showed complete resolution of both abscesses (Figures 3a, b) and the patient's symptoms resolved at three months during follow-up with mild referred otalgia on full mouth opening or yawning. Trismus improved measuring over two cm mouth opening. The patient is well-healed and improved overall. Informed consent for this case report was obtained from the patient.

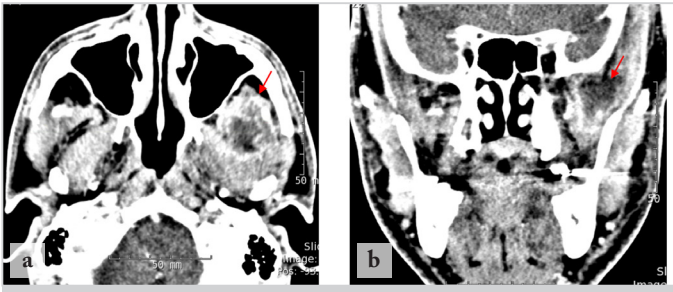

Figure 1. Preoperative CT scans: **a.** Axial CT view showing the clear borders of a 21x19 mm abscess in the left infratemporal fossa along the temporalis muscle with surrounding edema and inflammatory changes. **b.** Coronal CT view of the left infratemporal fossa abscess
CT: Computed tomography

Discussion

Abscess drainage using image-guided techniques such as ultrasound is widely accepted for superficial abscesses. However, ultrasound is limited for deeper locations, such as in the ITF, as was in our case. The 3-dimensional view provided by CT-guided navigation minimizes dissection and the risk of injury to nearby neurovascular structures and enables a precise surgical approach with a minimal error range (7, 9). Precision is crucial in our case as important

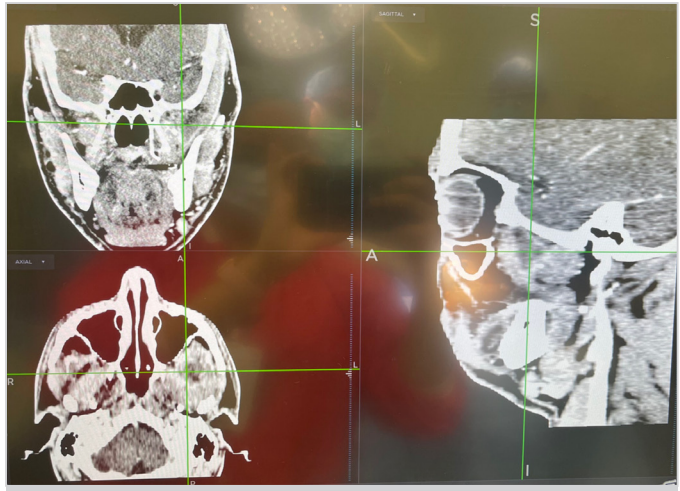

Figure 2. Intraoperative CT-guidance imaging: The image-guided Frazier tip suction and probe are shown in the infratemporal fossa abscess under live image localization using intraoperative CT-guided imaging in coronal, axial, and sagittal views
CT: Computed tomography

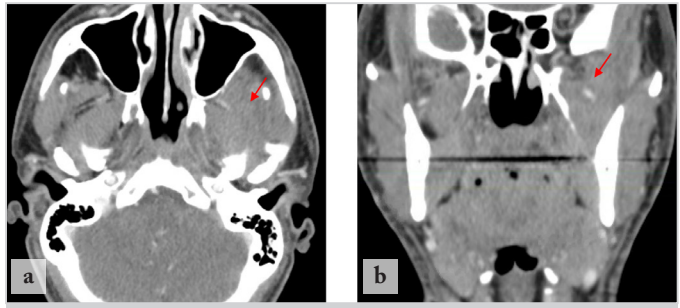

Figure 3. CT scans post-operation: **a.** Axial CT view showing complete resolution of the infratemporal fossa abscess. **b.** Coronal CT view showing complete resolution of the infratemporal fossa abscess
CT: Computed tomography

anatomical structures surround the surgical site including the inferior alveolar bundle, lingual nerve, second branch of the trigeminal nerve, internal maxillary artery, pterygoid plexus of veins, and posterior temporal artery. In our case, image guidance facilitated a minimally invasive trans-oral "keen" approach by allowing for the precise location of the abscess. On initial dissection, without the use of the image-guided probe, localizing the relatively small fluid collection was very difficult. CT-guided navigation allowed us to confirm the location of the abscess in real-time using the seeker tracker to accurately drain it. Without image-guided technology, this infection likely would have necessitated an open Gillies trans-temporal approach with heightened risk to the frontal branch of the facial nerve. CT-guided imaging can assist in the drainage of deep neck abscesses that are difficult to locate and surrounded by vital anatomical structures. Due to the critical neurovascular structures traversing the ITF, this space should always be entered bluntly with the utmost surgical precision and care.

There are a few limitations to the widespread utilization of the technology for this purpose. Registration errors and inaccuracy are very small with the current technology, accurate to within a few millimeters. Registration is flexible and may be centered to focus on the desired location, making risks of injuring the surrounding neurovascular structures minimal. Surgeons instrumenting the deep neck spaces should also consider magnetic resonance imaging-guided technology, when available, to better delineate critical neurovasculature. Cost is certainly worth noting, although once the technology is purchased, the individual cost per use is limited. Since many centers have already implemented CT-guided technology for use in endoscopic sinus surgery, the availability of the hardware should prompt an expansion in its indications. While indications for this approach should be dictated by the surgeon's experience and expertise, DNSIs which often require only cannulation and blunt dissection rather than surgical excision are most appropriate for "blind" image-guided dissection. Surgeons should approach ITF pathology, such as tumors that require excision, through an extended transnasal transpterygoid endoscopic approach or through an open approach as classified by Fisch. There has been one other report of using a CT-guided imaging system intraoperatively for the treatment of a pterygomandibular abscess after a failed surgical drainage attempt using an intraoral approach in 2018 (10). However, numerous examples of CT are being used in the head and neck region for abscess diagnosis and drainage.

Conclusion

In patients requiring re-operation for recurrent or difficult-to-treat abscesses, the surgeon should consider image-guided technology as a potential adjunct for intraoperative localization. CT-guided imaging can assist in localizing and protecting vital anatomical structures during deep neck abscess drainage.

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.J.U., S.Al-K., Concept: A.M., M.J.U., S.Al-K., Design: A.M., M.J.U., S.Al-K., Data Collection and/or Processing: A.M., M.J.U., Analysis and/or Interpretation: A.M., M.J.U., Literature Search: A.M., M.J.U., Writing: A.M., M.J.U.

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

- Infratemporal abscess is a difficult localization for drainage.
- Computed tomography (CT)-guided surgery is a recent innovative tool for infratemporal fossa abscess drainage.
- The primary objective of this work is to report on the minimally invasive approach and review the role of image-guided surgery in the management of deep neck space infections.
- We explore the presentation and unique CT-guided surgical management of an infratemporal fossa abscess in a 48-year-old male.
- Intraoperative CT-guided imaging can assist in localizing and protecting vital anatomical structures during deep neck abscess drainage.

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Endoscope-Assisted Removal of Post-Traumatic Orbital Epidermoid Inclusion Cyst: A Useful Adjunct

Case Report

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Abstract

Orbital epidermoid cysts are uncommon lesions within the bony orbit with varied symptomatology related to both the eye and the sino-nasal system. They are often slow-growing cystic masses which may cause facial asymmetry and visual loss due to pressure symptoms. Cross-sectional imaging such as computed tomography and magnetic resonance imaging are contributory and useful for assessment of the size and actual extent and should be mandatory before planning any surgical intervention. Open approaches and needle aspiration have been traditionally described; however, the use of the rigid nasal endoscope in the intraorbital compartment is a useful adjunct for exploration of the extent of the lesion and for complete surgical clearance. In this report, a 69 years old female with an old post- traumatic orbital epidermoid cyst which was removed completely using an endoscope via transorbital route was presented with the review of literature.

Keywords: Orbit, epidermoid cyst, proptosis, inclusion cyst, surgery, transorbital endoscopic surgery, case report

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Cite this article as: *Chowdhary S, Thangavel S, Lakshmanan J, Saxena SK. Endoscope-Assisted Removal of Post-Traumatic Orbital Epidermoid Inclusion Cyst: A Useful Adjunct. Turk Arch Otorhinolaryngol 2023; 61(2): 95-98*

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Received Date: 01.11.2022
Accepted Date: 02.03.2023

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DOI: 10.4274/tao.2023.2022-10-14

Introduction

Sino-orbital masses often present with proptosis and swellings involving the bony orbit and the sinonasal system. Both benign and malignant lesions within the orbit have similar presentations; hence they constitute a diagnostic challenge for the otolaryngologist and the ophthalmologist alike. Orbital epidermoid inclusion cysts are one type of deep-seated lesion that lies adjacent to critical anatomical structures; therefore, radiological evaluation followed by surgical intervention is the standard of care. Open approaches have been advocated for removal. However, for complete cyst enucleation or marsupialization, combined endoscopic and open approaches may be superior to either approach alone. The authors present a case of an old traumatic epidermoid inclusion cyst of the orbit, which was operated on successfully by a combined approach. The use of the endoscope to ensure a good surgical view in narrow restricted corridors such as the orbit enhances visualization and reduces chances of leaving behind residual cyst wall.

Case Presentation

A 69-years-old female presented with complaints of left-sided gradual diminution of vision for two years along with a progressively enlarging swelling along the

lateral aspect of the left eye with protrusion of the left eye for the past six months. It was painless initially, but she had gradually developed left retro-orbital pain. The patient had a history of blunt trauma to the left eye fifteen years back, which had been treated uneventfully. On local examination, significant left-sided relative non-axial proptosis of 9 mm was noted, and the left eyeball appeared to be pushed infero-medially. Her corrected visual acuity was 6/60 in the right eye and 3/60 in the left eye (Snellen's chart). Extraocular movements in the left eye were restricted. Color vision and fundus examination were normal. Her hematological parameters were normal. Computed tomography (CT) scanning revealed an oval, homogenous, smooth-walled lesion occupying the supero-lateral region within the left orbit, arising from the extraconal compartment pushing the eyeball inwards and inferiorly (Figure 1).

A contrast-enhanced magnetic resonance imaging (MRI) of the brain with the nose, paranasal sinuses, and orbit sections showed a single, lobulated, cystic mass of 3.4x2.3x3.9 cm in the left extraconal intraorbital compartment, which was hypointense on T1 sequences and hyperintense on T2 sequences, with diffusion restriction. The lesion abutted the superior rectus, superior oblique, and lateral rectus muscles. There was a thin, maintained fat plane between the lesion and the optic nerve, with scalloping of the orbital walls. An absence of post-contrast enhancement of the lesion confirmed its cystic nature (Figure 2).

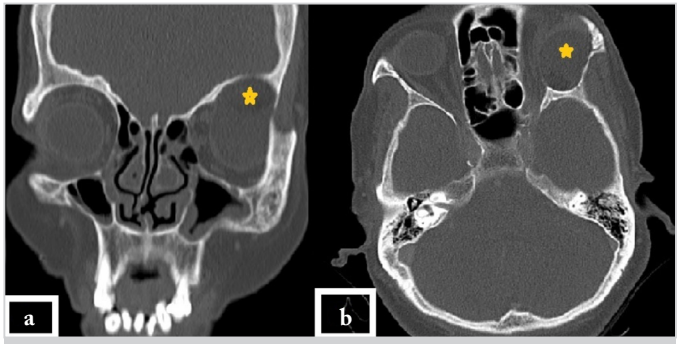

Figure 1. Preoperative computed tomography scan of the patient depicting the cyst location (yellow asterisk) within the intraorbital compartment. a) Coronal view, and b) Axial view

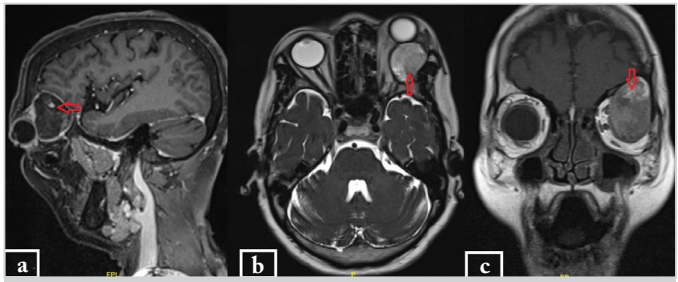

Figure 2. Preoperative contrast-enhanced magnetic resonance imaging depicting the cyst (red arrow). a) T1 sagittal, b) T2 axial, c) T2 coronal. A small region of T1 hyperintensity is seen within the posterosuperior aspect of the lesion, suggestive of probable blood within the cyst

Excision of the cystic mass under general anesthesia via an external approach was planned for the patient. A skin crease incision was made over the left orbit's eyelid on the supero-lateral aspect. After incising the orbicularis oculi, the thick membranous cyst wall was noted, which was adhered to the periosteum superiorly and periorbita medially. The cyst content could not be appreciated well and the posterior extent of the cyst wall was not seen. To avoid inadvertent incomplete removal, we decided to introduce a rigid endoscope (zero-degree, 4 mm, 18 cm) through the external incision to complete the procedure. Thick pultaceous material was suctioned out after introducing the endoscope. The cyst wall was removed piecemeal without violating the periorbita or the globe. Absence of any residual fragments of the cyst was confirmed. A clinical diagnosis of the epidermoid cyst was made. The cosmetic deformity was resolved postoperatively, and she continues to be on follow-up (Figures 3, 4). On one month follow-up, she had improved vision and resolved proptosis. Informed consent was taken from the patient for this case report.

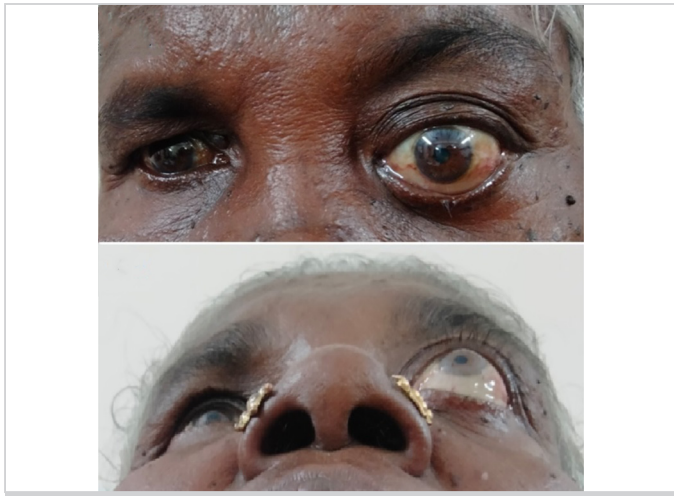

Figure 3. Preoperative patient photograph showing the clinical extent of the proptosis

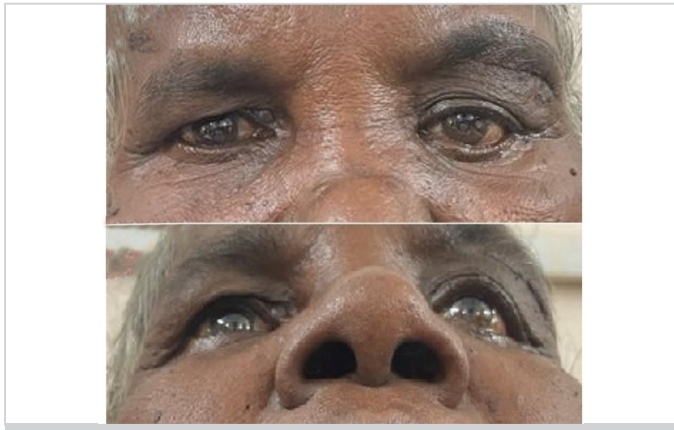

Figure 4. Postoperative patient photograph depicting the resolution of the symptom

Discussion

Intraorbital masses always pose a diagnostic challenge to both ophthalmologists and otolaryngologists due to the diversity of the possible lesions ranging from inflammatory abscesses and pseudo tumors to malignant masses. These lesions vary depending on their location in the orbit and present with various clinical and radiological features. Lesions within the orbit may have origins in the nose and paranasal sinuses (1), causing clinical dilemmas. Though proptosis is the most common presentation of orbital masses, they also present with pain in the orbit when deep-seated, and diplopia and sometimes diminution and restriction of the field of vision are present.

Epidermoid cysts of the lid and the orbit are extremely rare. They can be acquired or congenital. Acquired epidermal inclusion cysts are post-traumatic in origin due to the inclusion or implantation of epidermal, cutaneous, lacrimal or conjunctival elements into the dermis, especially after trauma (2). Post-traumatic or secondary inclusion cysts are typically seen in the areas of the body prone to maximal repeated trauma; hence, the intraorbital space is a rare site for its occurrence. Typically, epidermoid cysts contain a capsule that can be separated from its surrounding tissues and consists of inspissated keratin and whitish debris (3).

The painless, slow growth of orbital epidermoid inclusion cysts and their delayed presentation after the trauma often lead to confusion in clinical diagnosis. Entities like mucoceles, thyroid ophthalmopathy, or lacrimal system tumors give rise to a similar presentation. Such lesions can grow through the bony orbit and extend into nearby spaces such as the paranasal sinuses. Epidermoid cysts can also give rise to pain if they impinge on a deep-seated sensory nerve. Hence imaging is mandatory for ruling out other such lesions, whose managements differ significantly (4).

CT and MRI with contrast are the imaging modalities used to assess these lesions to formulate a definitive surgical plan based on extent and location. CT depicts a hypodense smooth lesion, with rim enhancement in case of abscess formation. An open biopsy or aspiration cytology can be attempted, but surgical extirpation is required to obtain tissue for histopathology and to correct the mechanical component of proptosis. The primary treatment modality is surgical removal because of the rare possibility of malignant transformation. Orbital lesions should be approached based on their location within the orbit. Open methods such as orbitotomy and craniotomy have been advocated (5, 6). However, a combined open and endoscopic approach provided superior visualization in our case. After skin incision and entry into the orbit, the introduction of the zero-degree endoscope into the cavity through the external incision allowed more space for suction of the contents, inspection of the cyst wall, and complete marsupialization and scraping of the cyst capsule from the orbital walls (Figure 5).

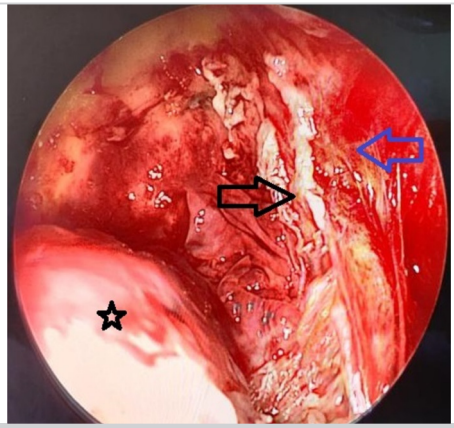

Figure 5. Intraoperative endoscopic view with a zero-degree endoscope depicting the globe (black asterisk), the lateral orbital wall (blue arrow), and the cyst wall (black arrow)

Moreover, the endoscope provides superior magnification in the narrow approach tunnel created by our lateral orbitotomy, thus reduces the chances of failure of the surgery. Similar to our approach, in their article Kashkouli et al. (7) mention that they used endoscopy in addition to open surgery to remove lateral orbital cystic dermoid cysts in six cases. They stated that a superior orbitomy via the eyelid was not ideal to introduce an endoscope because of the possibility of injury to globe contents. In cases requiring both endoscopic and open methods, various articles mention a cosmetically acceptable hairline incision or an incision over the calvarium at the pterion in combination with straight or angled scopes for maximizing access (8, 9). Furthermore, in our opinion, there is a reduced possibility of leaving behind any epithelium, which helps to avoid the future risk of a recurrence. Irrigation of the cavity was done afterward to flush out any possible remnants. Bipolar diathermy, in conjunction with the endoscope, was used to achieve hemostasis, as it is done in conventional endoscopic endonasal surgeries. There was no enophthalmos observed after the surgery in our case. An assistant is required to safely retract the globe medially to allow access. Large epidermoid cysts can be initially aspirated and decompressed to make space for the introduction of the endoscope.

In conclusion, post-traumatic orbital epidermoid cysts are rare, benign, mobile lesions that may evade diagnosis for years. Complementary approaches have been advocated for total removal (10). However, the endoscope is a useful tool for the exploration of the orbit through external incisions for better intraoperative clarity and management.

Conclusion

The causes of proptosis are many and diverse. Ophthalmologic, oncologic, and rhinologic causes should be considered, and appropriate investigations should be undertaken. Radiology is confirmatory for the diagnosis of intraorbital masses. The endoscope is a valuable tool

for exploring the extent and complete enucleation and marsupialization of the cyst in narrowly restricted areas such as the orbit. Traumatic implantation dermoid may evade diagnosis for years. Thorough history often provides a clue in this direction.

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.T., S.K.S., Concept: S.C., Design: S.C., S.T., J.L., S.K.S., Data Collection and/or Processing: S.C., S.T., Analysis and/or Interpretation: S.T., Literature Search: S.C., Writing: S.T., J.L.

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

- The causes of proptosis are many and diverse. Ophthalmologic, oncologic, and rhinologic causes should be considered, and appropriate investigations should be undertaken.
- Radiology is confirmatory for the diagnosis of intraorbital masses.
- The endoscope is a valuable tool for exploring the extent, and for a complete enucleation and marsupialization of the cyst in narrowly restricted areas such as the orbit.
- Traumatic implantation dermoid may evade diagnosis for years. Thorough history often provides a clue in this direction.

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Recurrent Pediatric Extranasopharyngeal Angiofibroma of the Epiglottis: Case Report

Case Report

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Abstract

Angiofibroma is a non-encapsulated, highly vascular tumor that usually originates in the nasopharynx. Laryngeal cases of extranasopharyngeal angiofibroma (ENA) are a very rare pathology, especially in children. Only eight ENA laryngeal cases have been described in the literature, and only one of them is a pediatric case. In this report we present an 11-year-old child with epiglottic ENA resected with transoral endoscopic ultrasonic surgery (TOUSS) with review of the literature. Because of reccurrence after five months he underwent re-excision with CO_2 laser. Recurrences in ENA are infrequent, but as demonstrated in our case, close endoscopic follow-up is mandatory in this location. Endoscopic hemostatic procedures like TOUSS and CO_2 laser ensure bloodless surgery for the management of this type of vascular laryngeal tumors.

Keywords: Angiofibroma, epiglottis, ultrasonic surgical procedures, laser therapy, pediatric, case report

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Cite this article as: *Hernando M, Lowy A, Agra C, Souvirón R, Pasamontes JA, Fernández-Fernández M. Recurrent Pediatric Extranasopharyngeal Angiofibroma of the Epiglottis: Case Report. Turk Arch Otorhinolaryngol 2023; 61(2): 99-102*

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Received Date: 22.02.2023
Accepted Date: 24.05.2023

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DOI: 10.4274/tao.2023.2023-2-10

Introduction

Angiofibroma is a non-encapsulated, highly vascular tumor that usually originates in the nasopharynx. Head and neck angiofibroma with an origin other than the nasopharynx [extranasopharyngeal angiofibroma (ENA)] is highly uncommon. Laryngeal cases are particularly unusual, especially in children (1).

Case Presentation

An 11-year-old male was referred to our institution with a six-week history of increased snoring, mild dysphagia and dysphonia without dyspnea. Flexible nasolaryngoscopy (FNL) revealed a 3-cm smooth, round, reddish lesion in the supraglottis (the laryngeal side of the epiglottis). An urgent computed tomography (CT) scan confirmed the presence of a polypoid mass likely originating from the laryngeal side of the epiglottis (Figure 1a).

Due to the patient's age, the possibility of endoscopic surgical access, CT findings, endoscopic evidence that it was a pediculated mass, and the availability of an ultrasonic scalpel for resection, we concluded that invasive diagnostic procedures such as angiography were not necessary.

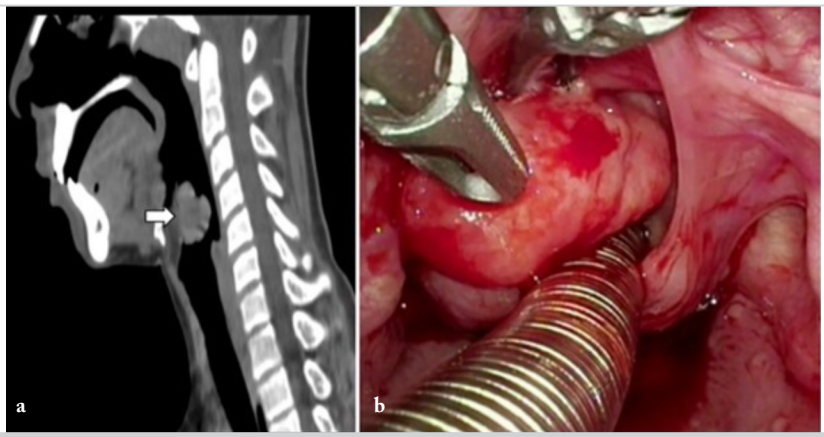

Figure 1. Original epiglottic tumor. a) Sagittal computed tomography with contrast that shows a polypoid solid lesion of 20.6x21.1x23.7 mm (white arrow) with an hyperdense periphery and a less dense center without epiglottic cartilage or pre-epiglottic fat involvement and without pathological adenopathy; b) Intraoperative endoscopic view of the epiglottis attached mass obstructing the supraglottic airway being resected with the grasping tip of the ultrasonic scalpel

We performed a complete resection using transoral endoscopic ultrasonic surgery (TOUSS) without a previous biopsy because of the child's airway compromise and the risk of profuse bleeding, bearing in mind that resection was going to be performed with a hemostatic method (Figures 1b, 2a). The postoperative course was uneventful and the patient was discharged after 24 hours once FNL confirmed the absence of laryngeal edema or airway compromise.

The histological description was a 3x2x2 cm diameter polypoid mass lined by smooth mucosa with focal ulceration that covered a soft tissue proliferation with numerous blood vessels with an attenuated smooth muscle layer and a thin endothelial layer with no atypia. The vessels often presented a staghorn shape, resembling that of a solitary fibrous tumor or hemangiopericytoma. Between the vessels, there was a dense, collagenous, fibrous stroma containing scattered plump, epithelioid or stellate fibroblasts with occasional mild nuclear atypia and no mitotic activity. Stromal cellularity varied and hyalinized nearly acellular areas were present in the center area. No malignant transformation, necrosis, mitotic activity or high cellularity were seen. Immunohistochemically, the stroma cells were positive for Actina HHF-35 and negative for desmin, CD34, STAT-6, S100, SOX10, myogenin, SM actin, beta catenin and estrogen or progesterone receptors (Figures 2b, c, d).

A possible recurrence of eight mm was found five months after the resection when FNL once more showed a supraglottic lesion. Revision surgery was performed by direct laryngoscopy with CO_2 laser. Again, the patient was discharged after 24 hours of uneventful postoperative follow-up (Figures 3a, b). Histopathological diagnosis was ENA again. After two years of follow-up, the patient remains disease free.

Informed consent form was signed by the parents of the patient to publish this case.

Discussion

ENA is an uncommon tumor whose clinical presentation differs from classic juvenile nasopharyngeal angiofibroma (JNA); therefore, they should be regarded as separate clinical entities. ENA can originate anywhere in the upper aerodigestive tract and there is a much more balanced gender ratio (2.13:1). It predominantly affects the nasal septum and often presents with faster-progressing symptoms (1).

An extensive Medline and Google systematic research by Windfuhr and Vent (1) in 2017, which included papers published up to 31 December 2015, reported 174 patients with ENA, and a male preponderancy of 66.1% and a median age of 23 years at diagnosis. Their findings included only 22 patients aged under 12 years, only one of them was epiglottic (2, 3). To our knowledge, only seven cases in children younger than 12 years have been published since Windfuhr and Vent's (1) review: two nasal septum ENA reports by Singh et al. (4) and Ganguly et al. (5), an oropharyngeal case by Gupta et al. (6), two inferior turbinate cases by Kim and Choi (7), an ethmoid case by Uwents et al. (8), and an inferior turbinate and lateral wall of nasopharynx case by Yan et al. (9).

The most frequent locations in pediatric cases were the nasal septum (30%), the maxilla (15%), the inferior turbinate (11%), and the ethmoid (11%).

Only eight ENA laryngeal cases have been described in the literature so far and only one of them is a pediatric case (in an 8-year-old child) described by Gołąbek et al. (2). In their case, the location was also epiglottic, but the tumor was smaller in size compared to our case (1.5 cm). Both patients developed the typical clinical manifestations of laryngeal involvement

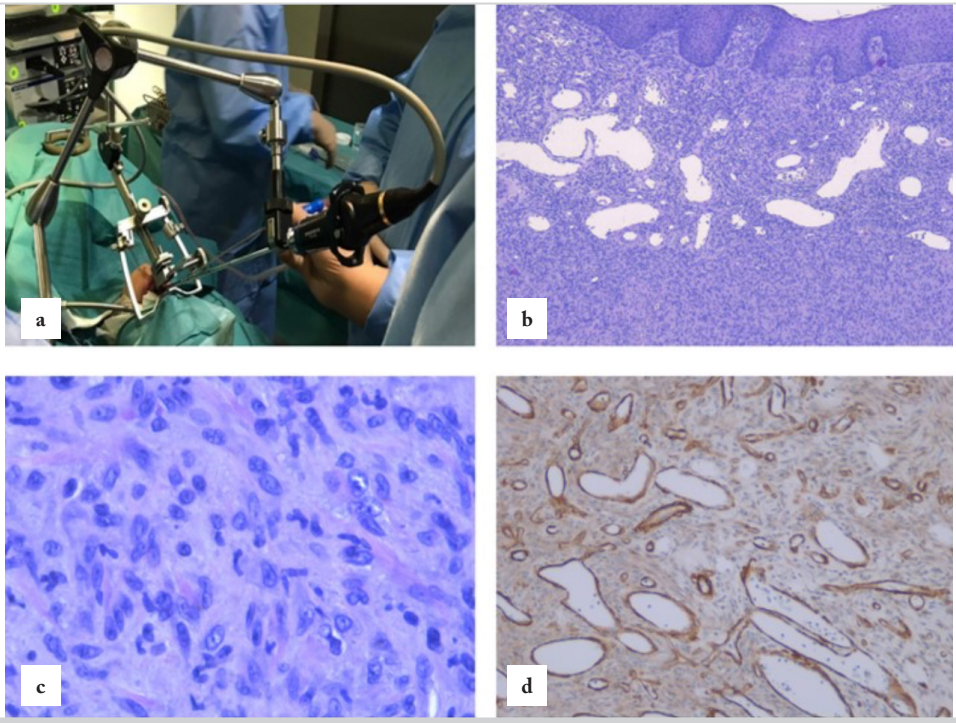

Figure 2. Transoral endoscopic ultrasonic surgery (TOUSS) and histological findings. a) TOUSS setup with retractor and scope holder; b) Hematoxylin & Eosin (H&E) (10X): Extranasopharyngeal angiofibroma presenting as a polypoid lesion. Sharply demarcated mass containing multiple vascular profiles. A non-specific superficial zone with squamous mucosa covers the luminal aspect of the tumor. Hemangiopericytoma-like abundant vascular pattern. c) H&E (40X): A higher magnification shows spindled cells containing uniform nuclei with delicate nucleoli. A coarse collagenous matrix is a consistent finding; d) IHQ for CD34 shows positivity in vascular channels and is negative in fusocellular components

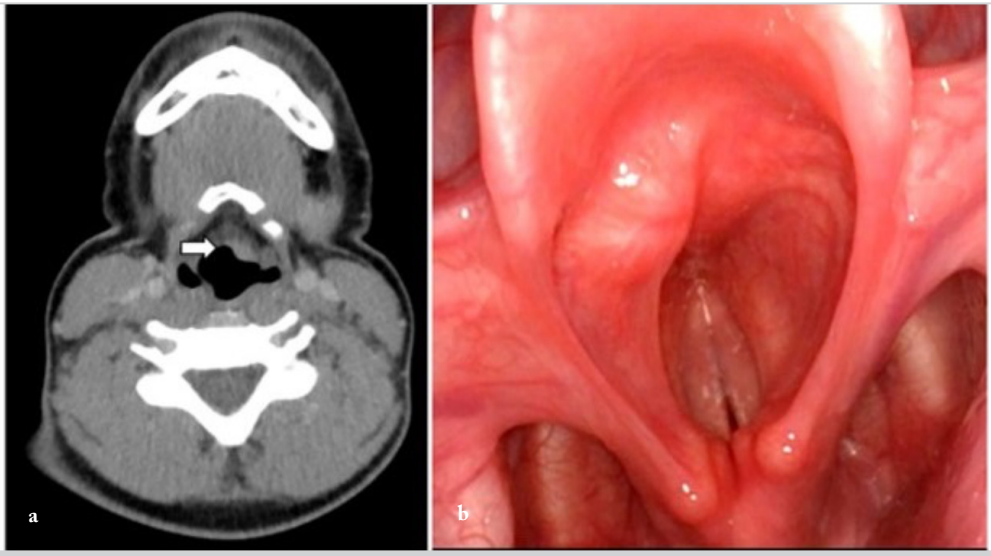

Figure 3. Fifth month recurrent tumor. a) Axial computed tomography with contrast showing a lesion of 5x5x8 mm with a moderate contrast enhancement in laryngeal epiglottic side (small white arrow); b) Endoscopic view of the recurrent lesion in outpatient control

such as hoarseness, muffled voice or dysphagia, as well as quick progressing symptoms [four weeks in Gołąbek et al.'s (2) case and six weeks in our case] unlike the two and a half years of progressive symptomatology reported in the previous supraglottic ENA cases in adults (10).

Hemostatic endoscopic procedures were used in our case. The original tumor was resected with the transoral endoscopic ultrasonic surgery technology, a non-robotic endoscopic, three-handed method using an ultrasonic scalpel as a resection tool (a 35-cm ThunderbeatTM) with high-definition 2D-3D endoscopic imaging with Olympus ENDOEYE Flex 5-mm 2D/10 mm 3D deflecting tip video laparoscopes (Figure 2a).

The recurrence was successfully excised with a CO_2 laser. Given that this recurrence was smaller in size (8 mm) than the original tumor (3 cm) and had a very sessile epiglottic

attachment, we thought that this limited the benefits of using an ultrasonic scalpel grasping tip and probably we would not be able to excise it without the risk of breaking the surgical piece and felt that a monobloc resection with laser was easier. There were previous successful excisions with this method in this location described in literature, too (2, 3).

The patient is now disease-free for two years after this second surgery with a close follow-up: first three months post-recurrence resection with monthly controls, then quarterly up to one year of control, and later biannual, all of them with FNL.

In contrast with nasopharyngeal angiofibroma, ENA recurrences were reported only in four patients included in Windfuhr and Vent's (1) systematic research; all of them within 12 months after diagnosis and only one in a pediatric case as early as two weeks after surgery (11).

We consider that our patient had the recurrence because there was a tumor growth following a complete monobloc excision. However, we know that the prevalent opinion in the recent JNA series is that most postsurgical recurrences are in fact cases of persistent disease due to incomplete excision and we cannot rule out that possibility in our case, even when the time to diagnosis was considerably long (five months) or having performed several endoscopies without evidence of the tumoral presence in this period.

Conclusion

Recurrences in ENA are infrequent but, as demonstrated with our case, a close follow up with FNL is mandatory in epiglottic locations until further experience is acquired with these rare tumors to help develop standardized protocols for their management.

Informed Consent: Informed consent form was signed by the parents of the patient to publish this case.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.H., A.L., R.S., J.A.P., M.F-F., Concept: M.H., A.L., C.A., R.S., J.A.P., M.F-F., Design: M.H., C.A., R.S., M.F-F., Data Collection and/or Processing: M.H., R.S., M.F-F., Analysis and/or Interpretation: M.H., A.L., C.A., J.A.P., M.F-F., Literature Search: M.H., A.L., J.A.P., Writing: M.H., A.L., M.F-F.

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

- Laryngeal cases of extranasopharyngeal angiofibroma (ENA) are a very rare pathology, especially in children.
- Recurrences in ENA are infrequent but, as demonstrated with our case, a close follow-up with flexible nasolaryngoscopy is recommended in epiglottic locations.
- In published epiglottic ENA cases, children have faster progressing symptoms than adults.
- Hemostatic surgical methods such as transoral endoscopic ultrasonic surgery or CO_2 laser may allow us to avoid invasive previous tests like angiography or partial biopsy in this type of vascular tumor.
- Given that recurrence is uncommon in this benign tumor and developed standardized protocols are not published, we decided to follow up the patient for two whole years.

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