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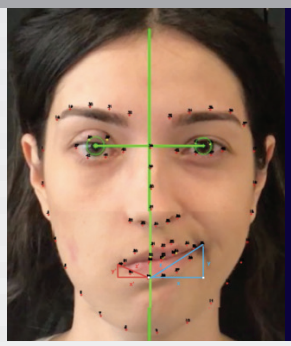

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AVES

Turkish Archives of Otorhinolaryngology
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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. The journal is released at three-month intervals, in March, June, September and December, and one volume of the journal comprises four issues. 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 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readers and experts concerning the published studies, articles about general practice and subject of the journal with historical content, memories of scientific significance, educative and catechetical manuscripts about medical deontology and publication ethics.

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 (doaj.org/bestpractice).

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Turkish Archives of Otorhinolaryngology

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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 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.

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

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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" targeting 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 important 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 Materials and Methods section and the statistical software that was used during the process must be specified.

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Table 1. Limitations for each manuscript type

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

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

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

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Detecting Intralabyrinthine Pressure Increase by Postural Manipulation with Wideband Tympanometry and Distortion Product Otoacoustic Emissions

Original Investigation

Emrah Yücel, Fazıl Necdet Ardıç, Funda Tümkaya, Cüneyt Orhan Kara, Bülent Topuz
Department of Otolaryngology, Pamukkale University School of Medicine, Denizli, Turkey

Abstract

Objective: Intracranial pressure increase is known to affect inner ear pressure through the cochlear and vestibular aqueducts. This finding forms a good model for inner ear pressure studies. Standard techniques used to detect this pressure increase are neither reliable nor easily repeatable or cheap. Studies with immitancemetry and otoacoustic emissions have been giving hopeful results. This study aims to confirm the results in the literature with wideband tympanometry and add a new parameter of otoacoustic emissions to inner ear pressure testing.

Methods: Wideband tympanometry (WBT) and distortion product otoacoustic emissions (DPOAE) tests were applied to 40 healthy participants in sitting, supine, and Trendelenburg positions. DPOAE were measured under ambient or peak pressure. Resonance frequency, tympanic peak pressure, 1000, 1500, 2000, 3000, 4000, and 6000 Hz frequencies in DPOAE were measured.

Results: The increase in the tympanic peak pressure and the decrease in resonance frequency (RF) due to position change were found statistically significant ($p<0.01$). Signal noise ratio (SNR) decrease at 1 kHz frequency and SNR increase at 2, 3, 6 kHz in the normal protocol, SNR decrease at 1 kHz in the pressurized protocol were found statistically significant ($p<0.01$).

Conclusion: RF in WBT and 1 kHz DPOAE SNR parameters were found useful in supporting the diagnosis in pathologies that increase intracranial pressure and inner ear pressure. Future research may ease their widespread use in clinical practice as they are non-invasive and rapidly applicable.

Keywords: Inner ear, resonance frequency analysis, tympanometry, otoacoustic emission, intracranial pressure

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Introduction

It is a well-known assumption that some of the inner ear diseases become symptomatic with the pressure change in the inner ear compartment. The most famous example is Ménière's disease. Besides Ménière's disease, viral, autoimmune, traumatic disorders of the inner ear may cause the same problem. Therefore, estimating the inner ear pressure accurately is an important goal in audiology. Up to now, electrocochleography, glycerol test, vestibular evoked myogenic potentials (VEMP), otoacoustic emissions (OAE), tympanic membrane displacement analyzer, three-dimensional fluid-attenuated recovery magnetic resonance imaging (MRI) with intratympanic or intravenous gadolinium were used for this purpose (1-4). The reliability, repeatability, and convenience of these methods have been studied continuously.

One of the first tests introduced for the inner ear pressure was electrocochleography (ECoG). Increased ratio of summating potential to the compound action potential over >0.40 is generally accepted as a significant sign of inner ear hydrops. Hornibrook et al. (1) tested patients with definite Ménière's disease and found that tone burst ECoG, click ECoG and MRI showed positivity in 83%, 30%, and 47% of the patients, respectively. Kahn et al. (2) reported that the sensitivity of VEMP was 43%, while sensitivity and specificity of 3 Tesla (3T) MRI intravenous (IV) contrast were 88% and 89%, respectively. The tympanic

membrane analyzer was sensitive to inter-individual differences, ossicular chain and middle ear status, and perforations of tympanic membrane. State-of-the-art MRI devices seem to provide the highest accuracy rate for detecting inner ear pressure increase; however, the technique is expensive, hard to repeat, and requires the use of contrast medium that may have side effects.

We still need simple, reliable, and easily repeatable tests. Some researchers focused on immittance tests for this purpose. When inner ear pressure increases, the stapes footplate moves towards the middle ear and stiffness of the annular ligament increases. This, in turn, increases the tension of the ossicular chain, thereby decreases middle ear compliance. All immittancemetric studies that aimed to measure inner ear pressure were based on this assumption (5). There are publications reporting using traditional 226 Hz tympanometry or multifrequency tympanometry (6, 7). It was reported that 2 kHz admittance graphs in the multifrequency tympanogram was affected most by the change of inner ear fluid mechanics. Multifrequency tympanometry (MFT) was believed to measure the pressure of perilymph in direct contact with stapes footplate. A decrease in resonance frequency (RF) and widening of the conductance tympanogram were also noted (4).

Wideband tympanometry (WBT) is a relatively new method. It is an immittancemetric test method that examines the sound transfer function of the middle ear. It uses click stimulus at a range of frequencies between 226 Hz to 8000 Hz (8, 9).

Several models have been used in inner ear pressure studies. One of these is the glycerol test. Glycerol is an osmotically active compound which reduces the water content of the inner ear and changes the osmolarity (10). The second method is manipulating the posture. Chapman et al. (11) showed that intracranial pressure changed when the posture changed. In two separate studies, Carlborg et al. (12, 13) carried out a series of experiments and reported that when the hydrostatic pressure in the subarachnoid space was manipulated, the pressure in the perilymphatic space was affected immediately when the cochlear aqueduct was open. When the cochlear duct was closed, the transfer time was delayed. They postulated that the endolymphatic sac and duct might play a role in this delayed pressure transfer when the cochlear aqueduct is closed. Arterial pressure has a little role in this mechanism. Hypobaric pressure was also a conditional effect depending on the rate of pressure change, patency of the cochlear aqueduct and the Eustachian tube. In another study, OAE was also subject to these experiments. A phase increase and level decrease were found especially at frequencies lower than 2 kHz (14). Preliminary studies also showed that posture change created a shift in hearing threshold, OAE, and middle ear impedance (15).

Main Points

- Postural change from sitting to Trendelenburg affects the inner ear.
- The possible mechanism is the reflection of intracranial pressure increase via the cochlear aqueduct.
- RF decreases and tympanic peak pressure increases with the postural change in wideband tympanometry.
- 1 kHz signal noise ratio decreases with the postural change in DPOAE.

This study aimed to confirm the results reported in the literature for wideband tympanometry and add a new parameter of otoacoustic emissions to inner ear pressure testing in healthy adults.

Methods

Subjects

Forty healthy adult volunteers were included in the study. All volunteers underwent detailed otolaryngologic examination. Those with normal ear examination, normal middle ear pressure with 226 Hz tympanometry, and a hearing threshold over 15 dB were included, and those with a history of ear disease, neurologic disorder, ototoxic drug use, and ear or cranial surgery were excluded. Volunteers were informed about the procedure and their consents were obtained in writing. The ethical approval of the study was obtained from the Pamukkale University Ethics Committee (Approval Date: February 26, 2016; Approval Number: 60116787-020/13170).

Intervention

Each ear of participants was measured individually, hence, a total of 80 ears were studied. All subjects were asked not to speak, cough, yawn, or gulp during the procedure.

WBT and OAE measurements were done in three positions, sitting (O), supine (S), and Trendelenburg (T) (15-20^0 head down position), using Titan clinical tympanometry (Titan Suite software; Interacoustics, Denmark). All tests were done immediately after position change.

WBT was performed by narrow band clicks for every 100 Hz at frequencies changing between 226 to 8000 Hz and pressure changing between +200 to -400 daPa. Resonance frequency (RF) at tympanic peak pressures (TPP) and pressure values were noted.

Distortion product OAE (DPOAE) was measured using f1 65 dB SPL, f2 55 dB SPL and f1/f2 ratio 1.22. Each test was done twice at ambient and middle ear peak pressure. DP-Gram of frequencies between 1-6 kHz were recorded. Signal noise ratio (SNR) of 1000, 1500, 2000, 3000, 4000, and 6000 Hz frequencies were used for comparison.

Statistical Analysis

SPSS version 12.0 (SPSS Inc.; Chicago, IL, USA) was used for statistical analysis. Continuous variables were noted as mean±standard deviation. Categorical variables were shown as numbers and percentages. The Kolmogorov-Smirnov test was used to analyze normal distribution, and as the distributions were not normal, nonparametric tests were used for statistical evaluation. A paired sample t-test was done for parametric vari-

ables. Friedman Test and Wilcoxon signed-rank tests were used for nonparametric variables. We considered p values <0.05 as statistically significant.

Results

A total of 80 ears of 40 volunteers were tested. Twenty-three (57.5%) were female and 17 (42.5%) were male. Their mean age was calculated as 28.32±6.

The average RF of 80 ears in O, S, and T positions were 867.68 Hz, 855.99 Hz and 849.99 Hz, respectively. The decrease in RF was found statistically significant (p<0.05) (Table 1). The average TPP for O, S, T positions were measured as -1.95, 7.63, 18.76 daPa, respectively. The increase was also found statistically significant (p<0.05) (Table 1). There were no statistical differences between right and left ears in RF and TPP.

DPOAE measurements were done under two pressure conditions: ambient and middle ear peak pressure. SNR decreased under an ambient pressure of 1 kHz, but increased at 2, 3, and 6 kHz with position changes. The changes in SNR, whether decreasing or increasing, at 1, 2, 3, 6 kHz were found statistically significant (p<0.05). But the differences in SNR values at 1.5 and 4 kHz were not significant (p>0.05) (Table 2). The right-left difference was only significant in 3 kHz in the sitting position. When we evaluated the DPOAE under peak pressure, only a decrease in 1 kHz SNR was found significant (Table 3). When we compared right and left ears, 3 kHz SNR under peak pressure was found statistically different in all positions.

Table 1. WBT measurements during postural change

	Sitting	Supine	Trendelenburg	p
Resonance frequency (Hz)	867.68±191.67	855.99±166.34	849.99±192.5	0.002
Tympanic peak pressure (daPa)	-1.95±8.51	7.63±9.69	18.76±12.77	0.0001

Table 2. DP-Grams under ambient pressure were measured and Signal to Noise Ratios were plotted on the table

	Sitting	Supine	Trendelenburg	p
1000 Hz	7.07±6.59	6.35±5.82	3.04±6.49	0.0001*
1500 Hz	16.96±6.5	17.54±6.56	16.87±6.5	0.181
2000 Hz	20.44±6.43	21.2±6.57	22.7±6.32	0.003*
3000 Hz	25.42±5.17	26.47±5.48	27.35±5.2	0.004*
4000 Hz	25.71±6.47	26.76±5.5	26.06±7.26	0.359
6000 Hz	29.65±5.89	30.2±5.68	31.2±6.03	0.007*

Table 3. DP-Grams under peak pressure were measured and signal to noise ratio values were plotted in the table

	Sitting	Supine	Trendelenburg	p
1000 Hz	7.85±6.08	6.24±4.97	4.01±6.72	0.0001*
1500 Hz	17.42±6.18	17.75±6.17	16.56±7.28	0.078
2000 Hz	20.9±6.07	21.62±6.21	22.41±6.76	0.056
3000 Hz	26.38±4.66	26.51±5.56	26.7±6.14	0.6
4000 Hz	27.04±5.68	26.52±5.12	26.5±5.93	0.62
6000 Hz	29.84±5.83	29.67±5.61	30.86±5.14	0.465

Discussion

In this study, we investigated the change in middle ear RF, TPP, and pressurized/ambient DPOAE while manipulating the pressure of CSF and inner ear by the postural change. We found that RF decreased and TPP increased when subjects changed from sitting position to the Trendelenburg position. Immediate measurements also showed that 1 kHz SNR decreased with position change under either ambient or peak pressure conditions. The 2, 3 and 6 kHz SNRs increase, but this increase was significant only under ambient pressure.

Normal RF value has been subject to investigations for a long time. Lutman (16) reported RF as 871 Hz in 1984. Kaya et al. (17) used MFT to measure RF in normal-hearing adults and found that RF was 1020.8 Hz in right ears and 978.3 Hz in left ears. Polat et al. (18) focused on the differences between genders and measured mean RF as 933 Hz and 992.5 Hz in males and females, respectively. They found this difference to be statistically significant. Another study that evaluated the gender and age differences reported that there were no statistical differences between genders and age groups except in 0-1-month-old babies. In this group, mean RF was detected as 330.4 in the right ear and 347.6 Hz in the left ear (19). We found the mean RF as 867.68±191.67 Hz in sitting position. In the literature, normal RF was reported to change between 800-1000 Hz. It was postulated that this wide range was due to the changing structure of the outer and middle ears according to age and hereditary traits (20).

WBT is superior to classic tympanometry in many aspects. But the lack of generally accepted normative values is an important limitation. WBT has been widely studied in middle ear diseases. But its capacity for detecting inner ear disorders has always drawn the attention of investigators. One of the major targets was Ménière's disease. To that end, different models were constructed to simulate inner ear pressure increase. One of these is position change. The assumption supporting the positional test with WBT is based on the interaction between the inner ear pressure and the cerebrospinal fluid (11). It has been postulated that when inner ear pressure increases, the stiffness of annular ligament increases, and elasticity of the ossicles decreases. This change could be measured with different techniques. RF is one of these. But there are conflicting results. Franco-Vidal et al. (21) investigated RF and the width of tympanogram change in MFT in different postural positions. When the position was changed from supine to Trendelenburg, the width increased from 141.7 daPa to 184 daPa and RF increased from 763.7 Hz to 795.8 Hz. The change in RF was found insignificant. In another study, same investigators found that RF decreased, and the width of 2 kHz tympanogram increased in Ménière's disease patients (4). So, they focused on

2 kHz tympanogram width and concluded that intracochlear pressure could increase between attacks in Ménière's disease (21). Sato et al. (22) tested patients with enlarged vestibular aqueduct syndrome (EVA). They found an RF decrease in EVA. The increase in endolymphatic volume and area of the third window were proposed mechanisms. Sugasawa et al. (23) compared Ménière's disease patients with normal and found decreased RF in Ménière's disease affected ears. They calculated the sensitivity and specificity as 41.3 and 84.2% when 875 Hz frequency was chosen as a cutoff point. The normal values in Sugasawa et al.'s (23) series were 1123±274.8 Hz, which was higher than ours. Kato et al. (24) also reported a good correlation between significant hydrops in MRI and 2 kHz tympanometry width. They concluded that peak width in MFT was an important indicator of Ménière's disease. They also found a tendency of decreasing RF with hydrops, but without any statistically significant difference (24). Cakir Cetin et al. (25), on the other hand, measured RF, absorbance and 2 kHz peak width during the acute attack of Ménière's disease and did not find any significant differences between the affected ears and the non-affected or control ears despite the tendency for increased RF in their results. We found a significant decrease in RF when position was changed from sitting to Trendelenburg. This finding showed that middle ear stiffness was not the only factor affecting RF change. Darrouzet et al. (5) claimed that RF was not only affected by the stiffness of the annular ligament, but also by the mechanical resistance of the inner ear.

DPOAE was also one of the proposed tests for inner ear pressure studies. Mom et al. (3) investigated the effects of glycerol and postural change in Ménière's disease with transient OAE and found that there was a positive phase shift in Ménière's disease patients, whereas this shift was inconsistent in the control group. Avan et al. (26) reported that phase shift in Ménière's disease patients was apparent below 1 kHz and increased with postural change, but not significantly, since Ménière's disease had already created a phase shift, postural change did not much affect the result. They also wrote that in 13 Ménière's disease patients, phase shift became normal in the asymptomatic period after having increased phase shift with the symptoms (26). Mom et al. (27) also evaluated the phase shift in Ménière's disease with postural change and reported that phase shift changed between -30^0 to $+45^0$ in healthy patients, and between -80^0 to $+145^0$ in Ménière's disease patients. Most of the studies in the literature worked with phase shift, but we evaluated the SNR from DPOAE and found that 1 kHz SNR decreased with the postural change measured either under ambient or peak pressure.

All the OAE studies agreed on the vulnerability or change in low frequencies. Also, in endolymphatic hydrops, hearing loss occurs starting from low frequencies. Densert et al. (28) proposed that hydrops might distort the basilar membrane and cause an abnormal asymmetry in hair cell conductance. Frank and Kössl (29) claimed that this might be due to the mechanical distortion of the outer hair cells only. We found a significant decrease in 1 kHz SNR under ambient and peak pressure with postural change. It was generally recommended that SNR had to be over 6 dB for good DPOAE measurement. Avan et al. (26) did not find any significant difference in SNR during their phase shift experiments. But all these hypotheses show that the basilar membrane and the outer hair cells are affected by the pressure increase. So, the increase of noise floor might be another parameter for detecting inner ear pressure.

Studies on measuring the changes in the inner ear pressure with immittancemetric tests and DPOAE also brought about a new approach estimating intracranial pressure. Spinal needles or intraventricular catheters are invasive techniques used for this purpose. Avan et al. (30) and Büki et al. (31) studied this subject on computer models, gerbil model, and human subjects, and reported that stiffness of annular ligament affected mostly 1 kHz in DPOAE phase. Experimental studies on cats showed that intracranial pressure immediately affected perilymphatic pressure when the cochlear aqueduct was open; whereas its transfer to the inner ear was delayed when the cochlear aqueduct was closed (13). The assumption and the results were impressive and gave hope for a new widespread application.

Conclusion

We found that RF decreased and TPP increased when the position of the subject was changed from sitting to Trendelenburg. We also found that especially 1 kHz SNR in DPOAE decreased with the same position change. The increase in other frequencies was not consistent with middle ear pressure change. The high variability of RF makes it hard to compare the results of different studies. Using right-left difference as a factor might be a more reliable criteria. We recommend the use of positional test with WBT in large cohorts before using it in clinical practice. Also, 1000 Hz DPOAE SNR is worth investigating in these subjects. Further studies in different patient groups with intracranial pressure increase will also enhance our understanding on the relationship between the cerebrospinal fluid and the inner ear.

Ethics Committee Approval: Ethics committee approval was received for this study from the Pamukkale University Ethics Committee (Approval Date: February 26, 2016; Approval Number: 60116787-020/13170).

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Balloon Laryngoplasty for Pediatric Subglottic Stenosis: A 5-year Experience

Original Investigation

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Abstract

Objective: The objective of this study was to present our experience and evaluate our results of endoscopic balloon laryngoplasty (BL) in children with subglottic stenosis (SGS) at a pediatric tertiary center over a 5-year period.

Methods: This study reviewed 41 pediatric patients diagnosed with acquired SGS who had undergone BL as the primary course of treatment. Cases were analyzed for details including patient demographics, SGS grade and length, timing and the type of surgery, presence of tracheostomy, comorbidities, postoperative management, complications and outcomes of balloon dilatation.

Results: Forty-one children (22 girls and 19 boys) who had undergone BL at a mean age of 26 months (range, 1 month to 14 years) were included in the study. Nineteen (46.3%) were diagnosed with acute SGS (12 thin stenosis, 7 thick stenosis) and 22 (53.7%) with chronic SGS (9 thin stenosis, 13 thick stenosis). The success rate of BL was 100% in patients with acute and chronic thin membranous stenosis. The effectiveness of BL was significantly higher in patients with acute thick stenosis than in patients with chronic thick stenosis (p=0.016).

Conclusion: This study confirms that BL in patients presenting with acquired SGS with thin membranous stenosis, regardless of whether acute or chronic, can have a good prognosis. However, the results are less promising in cases of chronic thick stenosis.

Keywords: Subglottic stenosis, balloon laryngoplasty, airway, pediatric, pediatric otolaryngology

Introduction

Subglottic stenosis (SGS) encompasses a range of potentially life-threatening conditions and is characterized by the narrowing of the airway below the vocal folds. SGS has an incidence reporting of 1 to 8% after endotracheal intubation (1). Advancements in neonatal care coupled with the introduction of prolonged intubation methods in neonatal and pediatric intensive care units have markedly reduced mortality rates in critically ill children over the last 60 years. Consequently, there is an increase in the incidence of SGS due to the application of mechanical ventilation (2, 3).

The treatment of SGS should be patient-centric with the utmost importance placed on all practices that aid in delivering successful surgeries. This involves a number of factors including the type of the stenosis, the surgeon's experience as well as the preferred course of treatment, expectations of the patient and the family, the quality of post-operative care the institution can provide, and the skill level of the caregivers (anesthesiologist, pulmonologist and gastroenterologist) (4).

The surgical techniques deployed fall into two groups, as endoscopic and open procedures. Laryngotracheal reconstruction, cricotracheal resection and cervical slide tracheoplasty feature prominently in the rankings for the frequently used open airway reconstruction procedures (3). However, the last 5-20 years, has seen the increased use of endoscopic approaches, especially after the introduction of the balloon dilator (4). Although balloon laryngoplasty (BL) has been used since the 1980s, it remains a relatively new technique in the treatment of SGS and is now heralded as an effective and less invasive treatment for appropriate stenosis cases (5).

The objective of this study was to present our experience and evaluate our results of endoscopic BL in children with SGS at a pediatric tertiary center over a 5-year period.

Methods

This is a retrospective review of all patients who presented with SGS, were diagnosed and referred to our tertiary care hospital between 2015 and 2020. Patient charts were analyzed and reviewed for data points, including patient demographics, grade of subglottic stenosis (Cotton-Myers classification (6)), timing (acute or chronic SGS; Avelino et al. (7)), craniocaudal extension of SGS

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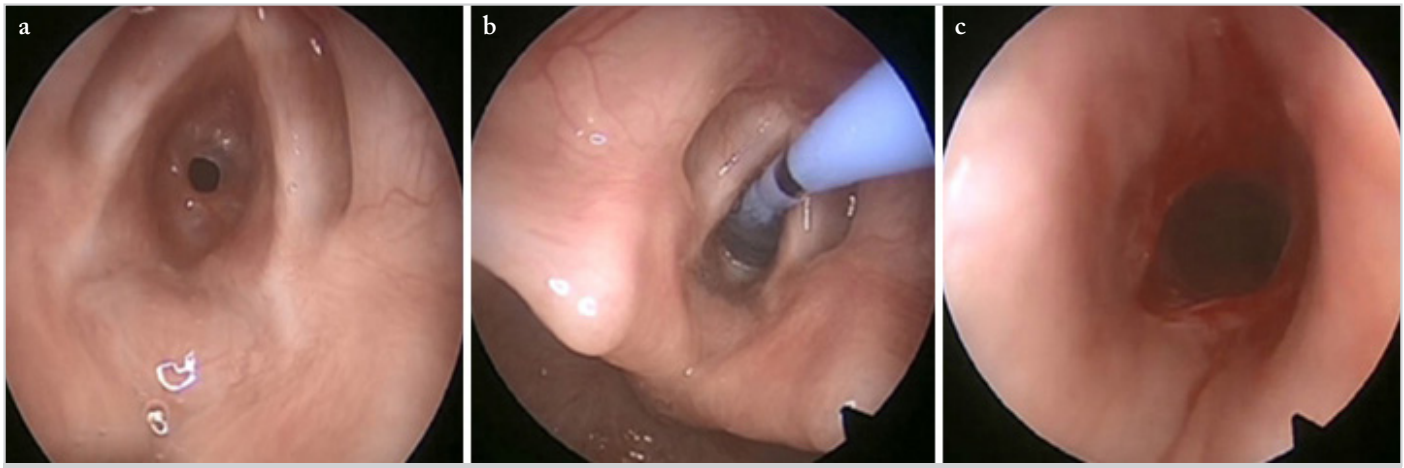

Figure 1. a-c. Acute grade III thin SGS in a 3-month old child. (a) pre-balloon laryngoplasty, (b) with balloon laryngoplasty, (c) post-balloon laryngoplasty

(thin or thick; McCaffrey classification (8)), type of surgery, presence of tracheotomy, comorbidities, postoperative management, complications, as well as the following outcomes: change in endoscopic grading of SGS, postoperative symptoms, rate of decannulation, tracheotomy status. Informed consent was taken from the parents. Local Ethics Committee of Ümraniye Training and Research Hospital approved the study (Approval Date: March 19, 2020; Approval Number: 7507).

This series included 41 pediatric patients with documented SGS who had undergone endoscopic BL as a primary modality of treatment. Patients who had other coexisting tracheal pathologic conditions, grade 4 SGS, SGS with glotto-subglottic stenosis, congenital SGS, previous intervention for their SGS, comorbidities requiring a high likelihood of prolonged ventilation in the future or lost to follow-up after treatment were excluded. The diagnosis and description of subglottic stenosis was performed by an expert pediatric otolaryngologist at the time of the direct laryngobronchoscopy (DLB) with spontaneous ventilation technique. The Myer-Cotton grade was used to assess the severity of SGS (6).

The timings of SGS were classified as follows.

1) Acute SGS was defined as a diagnosis of SGS within 30 days of extubation,
2) Chronic SGS was defined as a diagnosis of SGS 30 days after extubation (7).

The lengths of the scar tissue were classified as follows.

1) Thin SGS, which has a craniocaudal extension of <1 cm (McCaffrey classification grade 1)
2) Thick SGS, which has a craniocaudal extension of more than 1 cm and features either soft or hard scar contraction (McCaffrey classification grades 2 and 3) (8).

Main Points

- SGS is not a rare complication for the newborns or infants with prolonged intubation for various reasons in neonatal and pediatric intensive care units.
- SGS is a life-threatening condition.
- BL is a less invasive treatment for SGS.
- BL can have a good prognosis in patients with acquired SGS with thin stenosis regardless of whether acute or chronic.

Prior to BL, dynamic upper airway examination was performed under spontaneous respiration using a flexible bronchoscope (3.1 mm or 3.8 mm Olympus Medical Systems; Hamburg, Germany) in order to exclude the presence of possible additional airway diseases including laryngomalacia, vocal cord paralysis or tracheomalacia. DLB was performed under general anesthesia using a 0º rigid endoscope (Storz Corporation; Tuttlingen, Germany) with a diameter between 2.7 and 4 mm. After establishing the diagnosis, high-pressure balloon (Acclarent Technology; Boston, United States) was used and inflation pressure of 8-12 atm was maintained for 1 to 2 minutes or until the oxygen saturation level dropped below 90%. The balloon size was selected according to the theoretical ideal subglottic diameter for the patient's age (9). The procedure was performed three times each session. A pledget soaked with betamethasone dipropionate and gentamycin sulfate (Belogent; Farmatek, İstanbul, Turkey) was then applied to the dilated segment. Adjunctive procedure, such as radial divisions of stenosis was performed using cold knife in thick SGS featuring hard scar contraction. No patient was intubated after dilatation; instead, monitored in the pediatric intensive care unit for 24 to 48 hours. Follow-up endoscopy was performed after an interval of three weeks in all cases, and BL was performed when required. All patients received systemic steroids (Prednisolone; Actavis, İstanbul, Turkey) (1-2 mg/kg/d) for two days, proton pump inhibitors (Ulcuran; Avis, İstanbul, Turkey) for one month postoperatively. Follow-up DLB was performed three weeks after the initial DLB and the procedure was repeated until complete healing. After complete resolution of SGS, the children underwent a course of awake flexible fiberoptic laryngoscopy (FFL) every three months for a year. If the results were not satisfactory, BL was performed three times at 3-week intervals. If this failed to yield positive results, open surgery was performed. All DLB and awake FFL examinations were recorded (Figures 1, 2, 3, 4). Only when patients had been weaned from tracheotomy or had become symptom free for the duration of the study were deemed successful BL outcomes. The

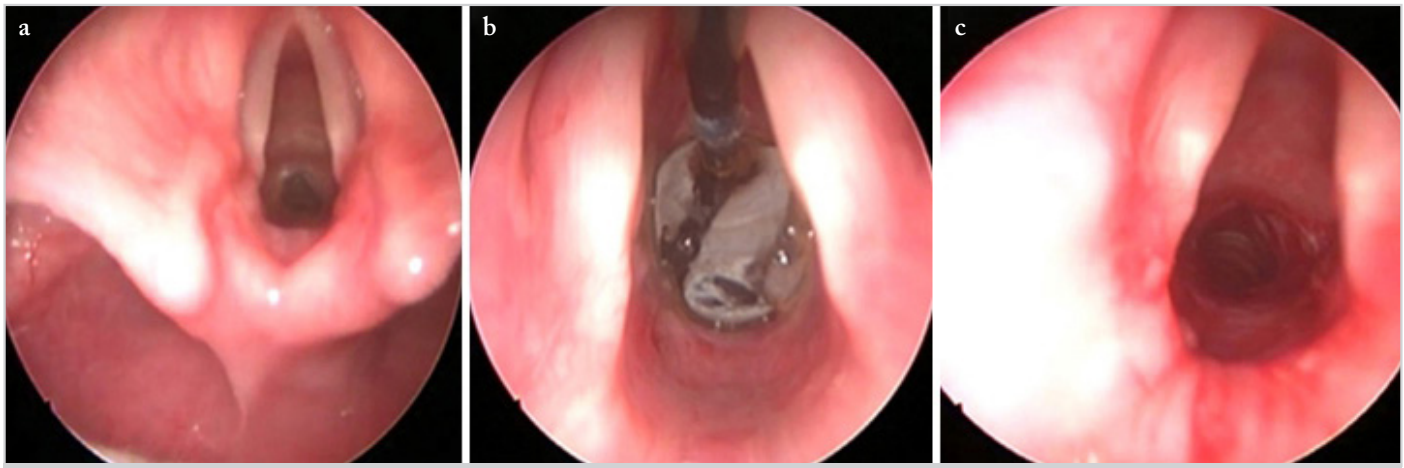

Figure 2. a-c. Acute grade II thick subglottic and tracheal stenosis in an 11-year-old child. (a) subglottic view of the lumen, (b) with balloon laryngoplasty, (c) post-balloon laryngoplasty

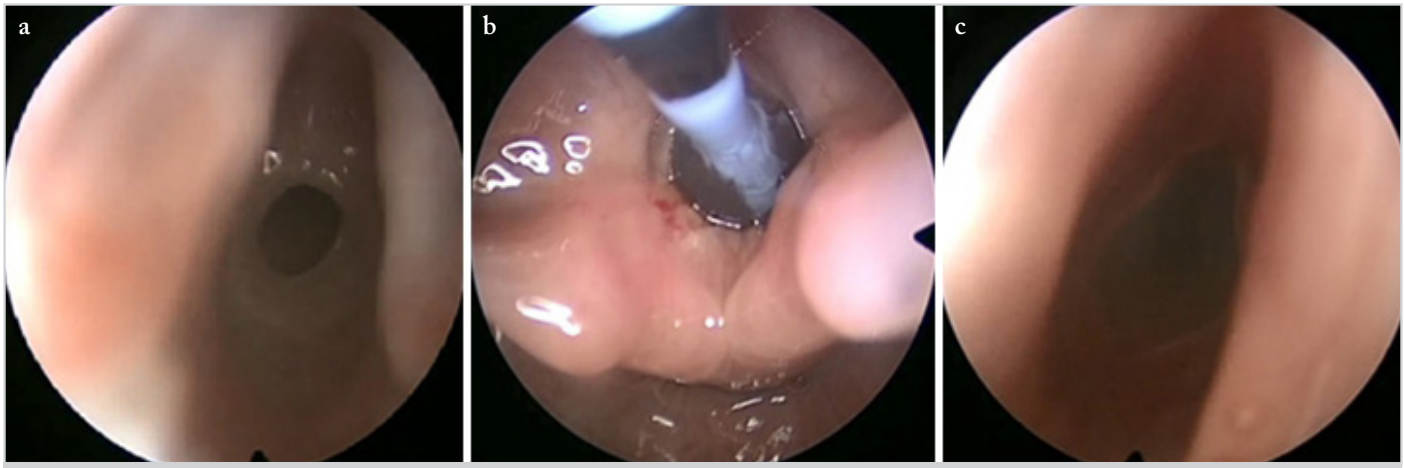

Figure 3. a-c. Chronic grade II thin SGS in a 7-month old child. (a) subglottic view of the lumen, (b) with balloon laryngoplasty, (c) post-balloon laryngoplasty

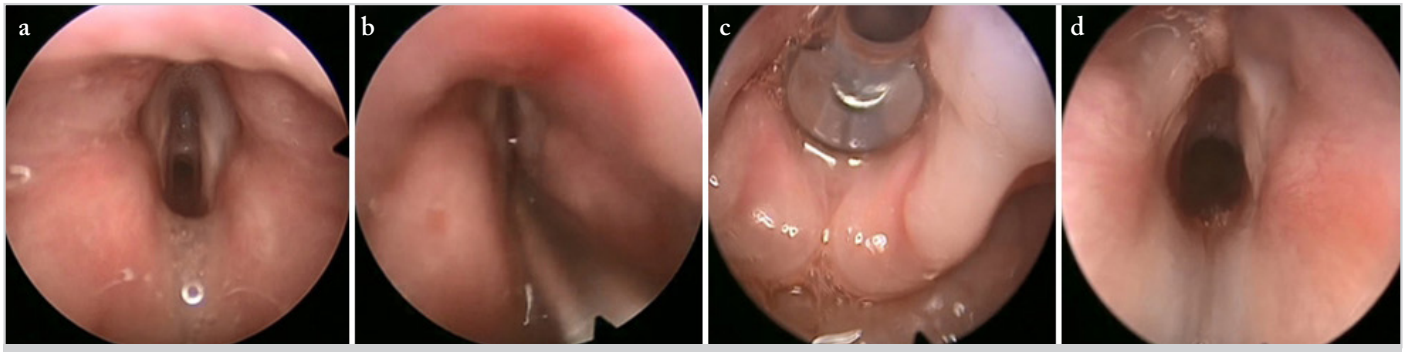

Figure 4. a-d. Chronic grade III thick SGS in a 22-month old child (a) subglottic view of the lumen, (b) radial divisions of stenosis using cold knife, (c) with balloon laryngoplasty, (d) post-balloon laryngoplasty

effectiveness of BL was calculated according to the changes in the Cotton-Myer grade with measurements taken before and after balloon dilatation.

Statistical Analysis

IBM Statistical Package for the Social Sciences version 20.0 (IBM SPSS Corp.; Armonk, NY, USA) was used for statistical analysis. The changes in the Cotton-Myer grades before and after the BL were compared using the Mann-Whitney U Test. P-values of ≤0.05 were regarded as significant.

Results

Forty-one children (22 girls and 19 boys) who had undergone BL, at a mean age of 26 months (range, one month to 14 years) were included in the study. Table 1 summarizes the breakdown of the patients by demographics, comorbidities, and details of

the etiology of stenosis. Nineteen (46.3%) children were diagnosed with acute SGS (12 thin stenosis, seven thick stenosis) and 22 (53.7%) with chronic SGS (nine thin stenosis, 13 thick stenosis). Thirteen patients had undergone a tracheotomy before laryngeal stenosis assessment. The mean period of follow-up was 15±8.6 months. The etiology pointed to all patients having developed SGS due to prolonged intubation. Other associated medical comorbidities were shown in Table 1.

Table 1. Demographics, comorbidities, etiology and follow up

	Patients (n=41)
Age range	1 month-14 years (mean: 26 months)
Gender	
Male	19 (46.3%)
Female	22 (53.7%)
Comorbidity	
Prematurity	11 (26.8%)
Only CHD	5 (12.1%)
Down syndrome + CHD	3 (7.3%)
CEA	1 (2.4%)
Type 1 DM	1 (2.4%)
None	20 (48.7%)
Etiology of SGS	
Prolonged intubation	41 (100%)
Mean follow up period	15±8.6 months

CHD: congenital heart disease; CEA: congenital esophageal atresia; DM: diabetes mellitus; SGS: subglottic stenosis

The details of the children regarding their SGS grade and other features were shown in Table 2. In patients with acute and chronic thin stenosis, the number of BLs ranged from one to two times. Moreover, the mean numbers of BLs in acute and chronic thin SGS groups were 1.3±0.7 and 1.2±0.4, respectively. However, in acute and chronic thick SGS groups this range was from two to three times. The mean numbers of BLs in acute and chronic thick SGS groups were 2.4±0.7 and 2.3±0.7, respectively. In all patients, BL was performed at 3-week intervals. The success rate of BL was 100% in patients with acute and chronic thin stenosis. In the acute thick SGS group (n=7) six children had undergone tracheotomies before BL and successful decannulation was achieved in two patients after balloon laryngoplasty. Three patients required additional open airway surgeries and the success rate of BL was four out of seven (57.1%). In the chronic thick SGS group (n=13) tracheotomy was performed in seven children before BL and one case was successfully decannulated after balloon laryngoplasty. Nine patients required additional open airway surgeries. In this group, the success rate of BL was four out of 13 (30.7%) (Table 2).

There was no significant statistical difference between the effectiveness of BL in patients with acute and chronic thin stenosis (p=0.56). BL was significantly more effective in patients with thin SGS (acute or chronic) than in patients with thick SGS (acute or chronic) (p=0.000). Moreover, the effectiveness of BL

Table 2. Comparison of outcomes between acute and chronic SGS

Type of SGS	**Acute (n=19)**		**Chronic (n=22)**	
Length of stenosis	**Thin stenosis (n=12)**	**Thick stenosis (n=7)**	**Thin stenosis (n=9)**	**Thick stenosis (n= 13)**
Pre-op grade*				
Grade I	-	-	11.1% (n=1)	7.6% (n=1)
Grade II	8.3% (n=1)	57.1% (n=4)	33.3% (n=3)	53.8% (n=7)
Grade III	91.7% (n=11)	42.9% (n=3)	55.5% (n=5)	38.4% (n=5)
Post-op grade*				
Grade 0	100% (n=12)	28.5% (n=2)	100% (n=9)	-
Grade I	-	42.8%(n=3)	-	23.1% (n=3)
Grade II	-	14.2% (n=1)	-	53.8% (n=7)
Grade III	-	14.2% (n=1)	-	23.1% (n=3)
Number of BL	1.3±0.7	2.4±0.7	1.2±0.4	2.3±0.75
Success rate of BL	100%	57.1%	100%	30.7%
Presence of tracheotomy	N/A	85.7% (n=6)	None	53.8% (n=7)
Decannulation rate after BL	N/A	33.3% (n=2)	None	14.2% (n=1)

*Cotton-Myer Classification
BL: balloon laryngoplasty; SGS: subglottic stenosis

was significantly higher in patients with acute thick stenosis than in patients with chronic thick stenosis (p=0.016).

There were no significant clinical complications related to the procedures.

Discussion

Airway narrowing in children is mostly located in the subglottis. The most expected pathogenesis of acquired SGS commences with subglottic mucosal pressure necrosis due to endotracheal intubation, then mucosal ulceration, followed by perichondritis, and finally mature scar tissue formation (10). This condition necessitates immediate treatment on symptom presentation. The purpose of BL is to arrest the progress of mature scar formation during the evolution of acquired SGS.

The lack of prospective studies evaluating the effectiveness of balloon dilatation has come to mean that balloon dilatation is predominantly featured in discussions. Designing controlled studies comparing BL to other more conventional therapies is challenging due to patients having a wide range of comorbidities and lack of uniformity amongst airway patients (e.g., age, weight, gender, ethnicity, stenosis diameter, length, histology, neurologic functions, glottal status and comorbidities) (11). Consequently, case series are an important mechanism for experience sharing.

The presented case series included 41 pediatric patients with acquired SGS who had undergone BL. The subglottic stenosis cases were divided into four subgroups: acute thin stenosis, acute thick stenosis, chronic thin stenosis, and chronic thick stenosis. Our results revealed that the effectiveness of BL may vary depending on the type of the subglottic stenosis. This study adhered to the guidelines established by the previous reporting by McCaffrey (8) for the purposes of this case series, however, it should be stressed that SGS measurements can be subjective.

The management of SGS in children is a frustrating and distressing process both for the patients and their families. In acute cases, it is possible that several extubation attempts are unsuccessful or extubation is successful but the child ends up with severe respiratory distress. In chronic cases, the child has already had a tracheotomy or is receiving treatment for recurring laryngitis or asthma. According to several studies, the success rate of BL for acute SGS was significantly higher compared to chronic SGS (2,7). Avelino et al. (7) demonstrated a success rate of 100% for acute SGS and 39% for chronic SGS and determined that success rates could be linked to the SGS grade and the immature scar tissue. Lee et al. (2) suggested that patients with acquired SGS, once diagnosed, should promptly undergo balloon dilatation as it increases treatment success rates, and decannulation as well, to reduce the need of tracheotomies. However, Simpson et al. (12) warned that in patients with chronic acquired SGS, the prognosis could be worse if circumferential stenosis and scar contraction are present. In the presented study, balloon dilatation demonstrated a 100% success rate in patients with SGS with thin and soft membrane, regardless of whether the scar tissue was acute or chronic. This success rate was 57.1% in patients with acute thick stenosis and 30.4% in patients with chronic thick stenosis. These results reaffirmed that when the stenosis features thin and soft membranous scar tissue, regardless of whether acute or chronic, the success of balloon dilatation is virtually certain. If the stenosis is fibrotic and thick in character, prompt execution of balloon dilatation is paramount to ensure success, as the stenosis expands easier during the acute period than in the chronic period. Therefore, early diagnosis and treatment of acquired SGS is vital to prevent recurrence. Children who have undergone prolonged endotracheal intubation and develop stridor and respiratory distress after extubation need extra consideration and care.

On reviewing the literature, we found that one systematic review, which included 7 studies and 150 patients, estimated the overall success rate of BL as 65.3%. The authors claimed that failures may be linked to more severe grades of stenosis (13). In our series, the success rate was calculated by ignoring the types of stenosis and scar tissue. The presented study demonstated that where the grade of SGS is severe, the success of balloon dilatation is high in the patients with acute and chronic thin SGS. Moreover, this outcome shows that the nature of stenosis is more important than its grade.

There are varying numbers of dilatations reported in the literature. Some authors describe performing up to seven dilatations until achieving success, but most report that up to three dilatations were necessary for successful treatments (14). In our study, serial DLB was performed as previously described and deemed successful if there were any responses in the form of grading, extension, or clinical picture. If there was no improvement in the patient's condition after three consecutive sessions, we moved to open surgical procedures. For each patient with acute or chronic thin SGS, the number of BLs performed ranged from one to two times. In patients with acute and chronic thick SGS, however, this number ranged from two to three times. Unfortunately, the outcomes of three patients in the acute thick SGS group and nine patients in the chronic thick SGS group were not satisfactory.

Special attention should be devoted to balloon dilatation in children who have not undergone tracheotomy. Close collaboration with the anesthesiology team is vital in pediatric airway surgeries (15). Reported complications related to balloon dilatation of the lower airway include granuloma formation, mucosal laceration, tracheitis, bleeding, pneumothorax, pneumomediastinitis, atelectasis, and death (15). Furthermore, a rapid, complete luminal obstruction secondary to edema in response to balloon dilatation was reported by Gungor (16). This complication can cause an inability to intubate. All surgeons need to be alert about the presence of this complication should it arise, the occurrence of which would necessitate an emergency tracheotomy. The downside risks posed by BL can be managed by reviewing the location, the size of the stenosis, and by analyzing the patient's underlying health condition (15). In our study, none of the patients experienced any major complications from BL.

Conclusion

This study highlights the evidence that BL in pediatric patients with acquired thin SGS, regardless of whether of acute or chronic, can have a good prognosis. BL may be considered as a first-course treatment for thin acquired SGS. However, further research is advocated for its use in the management of SGS especially with thick and mature stenosis.

Ethics Committee Approval: Ethics committee approval was received for this study from the Local Ethics Committee of Ümraniye Training and Research Hospital (Approval Date: March 19, 2020; Approval Number: 7507).

Informed Consent: Informed consent was obtained from the parents of the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.Ş.Ö., Ö.G.; Design - S.Ş.Ö., Ö.G.; Supervision - A.Ş.Y., Ö.G.; Resources: Ö.G.; Materials - S.Ş.Ö., B.Y.; Data Collection and/or Processing - S.Ş.Ö., B.Y.; Analysis and/or Interpretation - S.Ş.Ö., B.Y.; Literature Search - S.Ş.Ö., A.Ş.Y., B.Y.; Writing - S.Ş.Ö., A.Ş.Y.; Critical Reviews - S.Ş.Ö., A.Ş.Y.

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Outcomes of Middle Turbinate Flap in the Reconstruction of Non-tumorous Ventral Skull Base Defects - an Institutional Review

Original Investigation

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Abstract

Objective: Middle turbinate (MT) flap, based on the branches of sphenopalatine artery is one of the commonest mucosal flaps used in endoscopic skull base surgery. The objective of this study is to analyze the outcomes of the MT flap in the reconstruction of non-tumorous ventral skull base defects.

Methods: A retrospective review of patients was done from 2010-19. Patients who underwent reconstruction for non-tumorous ventral skull base defects using middle turbinate (MT) flap were included in the study. The parameters assessed include patient demography, primary etiology, site of the defect, size of the defect, graft materials used, outcomes and postoperative complications.

Results: A total of 13 patients who met the study criteria were included. Three (23.07%) of the patients had meningo-encephalocele, while the remaining 10 (76.93%) had CSF fistula. Isolated foveal defect (53.8%) was the most common site involved, followed by isolated cribriform, combined cribriform-foveal and combined foveal-planar defects. Graft materials used were fascia lata, fat and septal cartilage. MT flap was successfully harvested in 11 (84.6%) patients, with successful outcome in 10/11 patients. Hypoplastic MT was present in two patients, who subsequently required Hadad flap for defect closure. No major complications were reported in the postoperative period.

Conclusion: The MT flap is effective in the reconstruction of selective skull base defects. Appropriate surgical technique and expertise are required for successful harvest. Further studies are required to analyze its outcomes in various skull base defects.

Keywords: Middle turbinate, skull base, surgical flap, reconstruction, endoscopic surgical procedure

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Introduction

Multi-layered reconstruction is preferred for reconstructing skull base defects associated with cerebrospinal fluid (CSF) rhinorrhoea. Mucosal flaps based on nasal septum, middle turbinate (MT) and inferior turbinate (IT) are the common intra-nasal flaps used for the reconstruction of skull base defects (1, 2). External incision and osteotomies are not required for harvesting these flaps, in contrary to pericranial and temporoparietal fascia flaps (3). Currently, nasoseptal flap based on the posterior septal artery (Hadad-Bassagasteguy) (HB) is the most popular and versatile flap used in ventral skull base reconstruction (4). However, many authors consider the dissection needed to harvest and use of HB flap as excessive for small to medium sized skull base defects.

The MT flap, based on the middle turbinate branch of the sphenopalatine artery is another robust flap used to repair small defects in the olfactory groove and sella (5). MT is a leaf like structure attached to the cribriform plate, lamina papyracea and perpendicular plate of palatine bone. As most of encephaloceles and CSF fistulas occur in cribriform and foveal areas, this flap can be considered in reconstructing the defects in these areas (6, 7). Smaller surface area and harvesting difficulties are considered as the main limitations of this flap. Very few studies are available in the literature describing the role of MT in skull base reconstruction. This study

was designed to analyze the outcomes of middle turbinate flaps in endoscopic reconstruction of non-tumorous ventral skull base defects.

Methods

Institutional ethical committee approval was obtained from Sri Ramachandra Institute of Higher Education and Research (Approval Date: February 17, 2020; Approval Number: 23/2020). Details of patients who underwent skull base reconstruction using MT flap in the period from 2010 to 2019 were collected from the medical records. Patients in whom other pedicled flaps were harvested because of a failed attempt to harvest the MT flap were also included in the study. These patients were included to analyze their causes of failure. The following details were analyzed from the records: demography, primary etiology, site of the defect, size of the defect, graft material used, presence of CSF leak during surgery, outcomes, and complications. The use of other vascular flaps and open craniotomy were considered as exclusion criteria and those patients were excluded from the study.

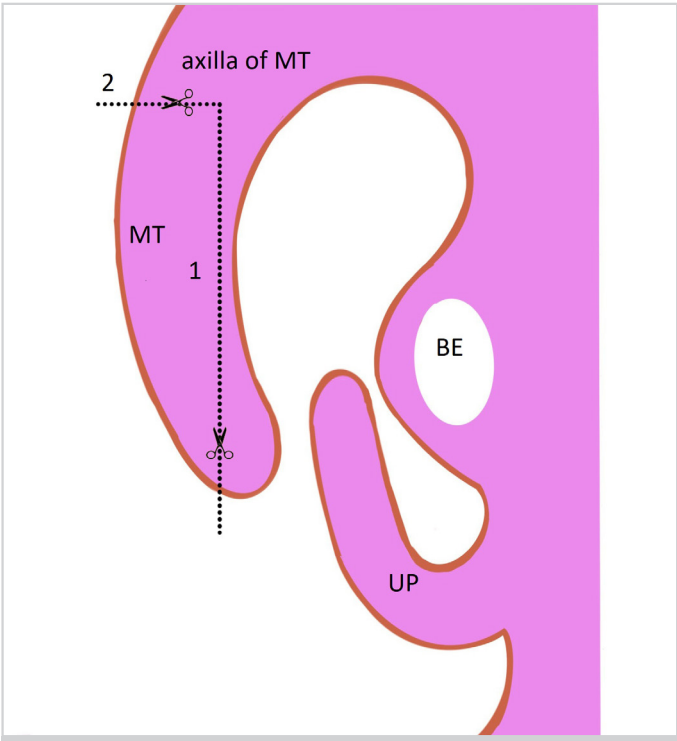

Figure 1. Diagrammatic representation of osteomeatal complex on left nasal cavity (coronal view)
*: represents the axilla of middle turbinate. Pink and brown shaded areas represent bony and mucoperiosteum, respectively. 1: represents the first vertical incision made over the caudal part of middle turbinate. 2: represents the horizontal incision made along the medial surface of middle turbinate
MT: middle turbinate; BE: bulla ethmoidalis; UP: uncinate process

Main Points

- Middle turbinate flap was successfully harvested in 11/13 (84.6%) patients. Hypoplastic middle turbinate was the cause for failure in two patients.
- Defect was successfully closed in 10/11 (90.9%) patients with no major complications.
- Middle turbinate flap can be effectively used in non-tumorous skull base defects with less morbidity.

Harvest of Middle Turbinate (MT) Flap

Written informed consent was obtained from all patients prior to their procedures. The MT flap was harvested based on the technique described by Prevedello et al (8). Under general anaesthesia, after positioning the patient, the nasal cavity was decongested using 1:1000 adrenaline patties. The MT was in-

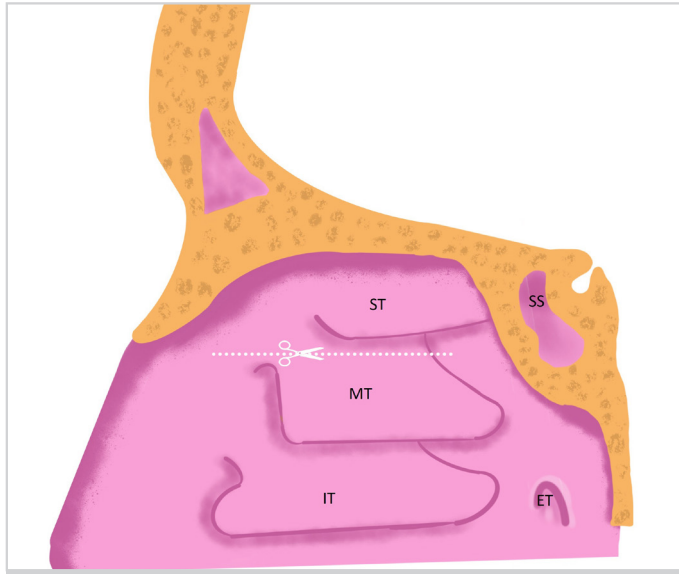

Figure 2. Diagram showing the horizontal incision extending along the medial surface of middle turbinate
ST: superior turbinate; MT: middle turbinate; IT: inferior turbinate

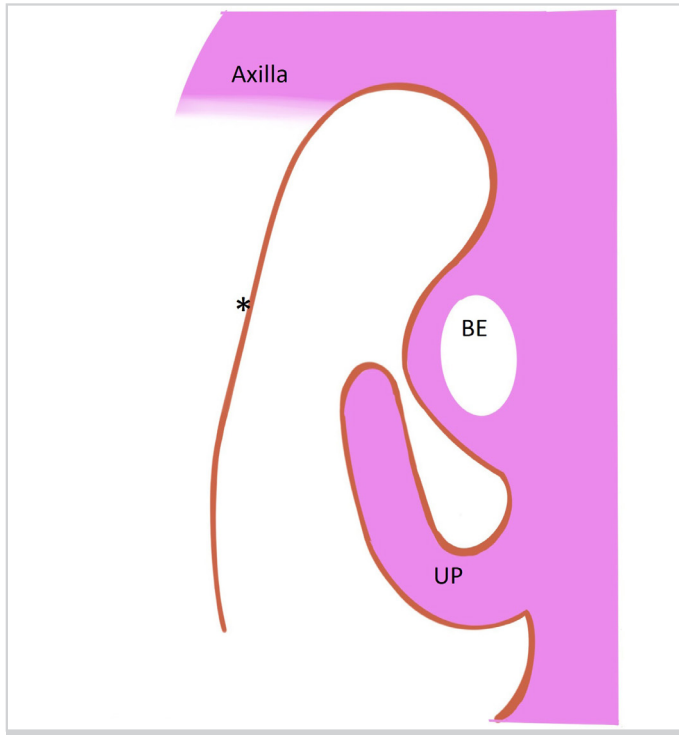

Figure 3. Diagram showing the vascularized MT flap attached to its pedicle after removal of bony segments of MT
MT: middle turbinate; BE: bulla ethmoidalis; UP: uncinate process.

filtrated using 2% xylocaine and adrenaline to facilitate hydrodissection. A vertical incision was made in the rostral part of the MT starting from the axilla. A second incision was made horizontally along the medial surface of the MT, close to its superior attachment, respecting the cribriform plate (Figures 1, 2). The mucoperiosteum was elevated and the bone was removed in piecemeal. The axilla was cut using endoscissors detaching the MT from the skull base. This cut was continued posteriorly up to the vascular pedicle. The mucoperiosteal flap remained attached only at its pedicle and unfolded like and open book (Figure 3). Prior to harvesting the flap, the maxillary sinus ostium was widened, and the sphenopalatine artery was identified at its exit point in the sphenopalatine foramen. The pedicled MT flap was rotated and placed either inside the maxillary sinus or the nasopharynx.

Once the flap was harvested, the primary etiology was addressed. The defects were delineated and repaired in multiple layers. Fascia lata was used in all cases, while fat and cartilage were used as grafts additionally in selected cases. The grafts were placed in the following order: at (in selected cases) followed by fascia lata (interlay-tucked between dura and bone), cartilage (in selected cases) and fascia lata (overlay-overlying the bone). If cartilage was not used, only one layer of fascia lata was used. The MT flap was reinforced over these graft layers which was further reinforced with oxidized regenerated cellulose strips (Surgicel, original haemostat, Ethicon; Mumbai, India) and fibrin sealant (Tisseel, Baxter; Westlake, California, USA) (Figure 4). The nasal cavity was packed, and the pack was removed after 48 hours. All patients received acetazolamide tablet 250 mg thrice a day in the postoperative period. No patients underwent lumbar drainage in the postoperative period.

Statistical Analysis

The data was entered and analyzed in MS-Excel software, version 2005. Qualitative data was expressed in percentages and quantitative data was expressed in mean±standard deviation.

Results

Demography

A total of 13 patients who satisfied the study criteria were included. The mean age of study cohort was 39.8±11.8 years. Male-to-female ratio in the study was 6:7 (Table 1).

Etiology

The primary etiology of the patients in this study were either meningo-encephalocele or CSF fistula. In three (23.07%) patients, meningo-encephalocele was the aetiology, while the remaining 10 (76.93%) had CSF fistula alone. None of the patients in the study cohort had tumor as primary etiology, and all defects following skull base tumor removal were reconstructed with HB flap or other pedicled vascular flaps.

Site and Size of the Defect

In this study, seven patients (53.8%) had isolated foveal defect, three patients (23.07%) had isolated cribriform defect, two patients (16.6%) had combined foveal and cribriform defect, and

Table 1. Table showing demographic details, defect area, size of defect, layers of reconstruction, outcome and follow up

Seq. no	Age	Sex	Primary etiology	Defect area	Size of the defect (cm^2)	Graft used	Outcome	Follow-up (months)
1	43	F	Meningo-encephalocele (without CSF leak)	Fovea	3.2	Fascia lata, Cartilage	Success	18
2	34	F	Spontaneous CSF leak	Fovea	3.2	Fat, Fascia lata, Cartilage	Failure, converted to HB flap	N/A
3	45	M	Traumatic CSF leak	Fovea	2.1	Fat, Fascia lata.	Success	24
4	32	M	Traumatic CSF leak	Cribriform and fovea	3.7	Fat, Fascia lata, Cartilage	Failure, converted to HB flap	N/A
5	36	F	Traumatic CSF leak	Cribriform	2.9	Fat, Fascia lata	Success	27
6	42	F	Spontaneous CSF leak	Cribriform	3.1	Fat, Fascia lata, Cartilage.	Failure	12
7	15	M	Traumatic CSF leak	Fovea	4.2	Fat, Fascia lata, Cartilage	Success	20
8	24	M	Meningo-encephalocele (without CSF leak)	Cribriform and fovea	4.5	Fascia lata, Cartilage	Success	17
9	34	F	Spontaneous CSF leak	Fovea	2.4	Fat, Fascia lata, Cartilage	Success	10
10	54	M	Traumatic CSF leak	Cribriform	3.9	Fat, Fascia lata, Cartilage	Success	12
11	45	F	Spontaneous CSF leak	Fovea	2.9	Fat, Fascia lata, Cartilage	Success	19
12	54	M	Meningo-encephalocele (without CSF leak)	Fovea and planum sphenoidale	3.1	Fascia lata, Cartilage	Success	23
13	46	F	Spontaneous CSF leak	Fovea	2.3	Fat, Fascia lata, Cartilage	Success	10

M: male; F: female; HB: Hadad-Bassagasteguy flap; CSF: cerebrospinal fluid; N/A: not applicable

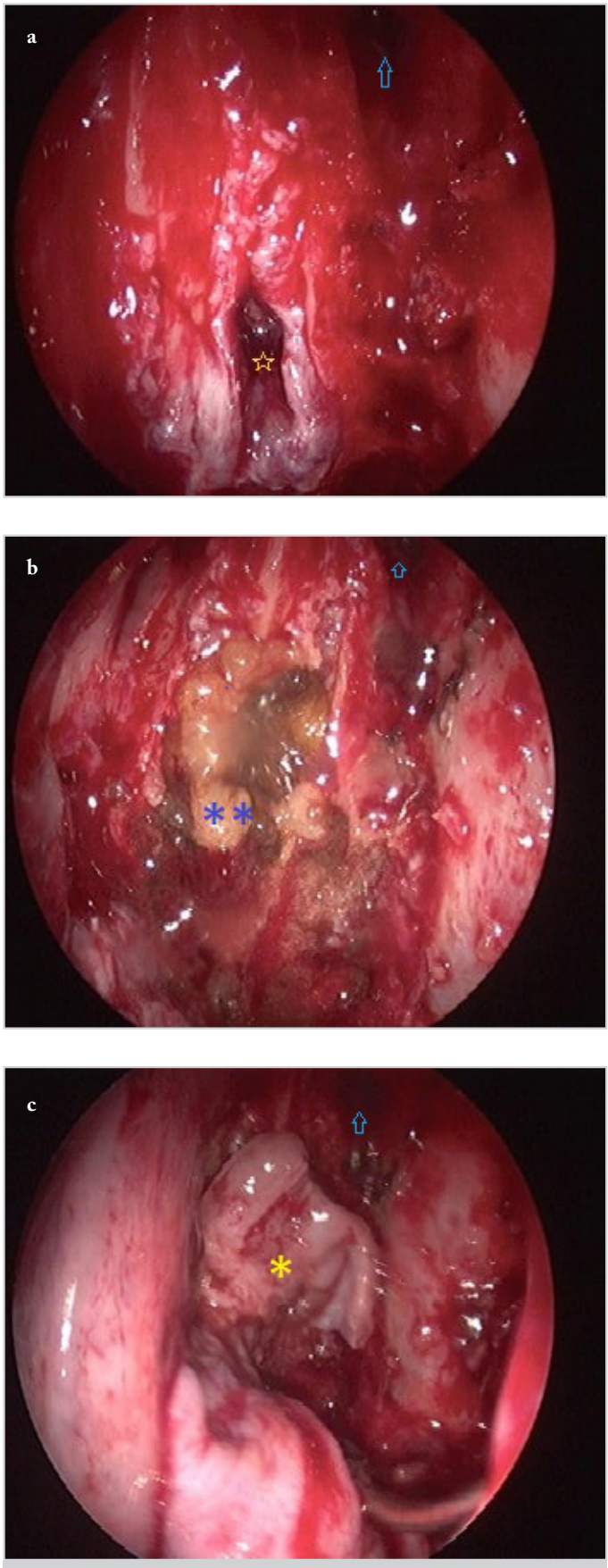

Figure 4. a-c. Intraoperative photographs showing (a) a defect in the cribriform plate of left nasal cavity, (b) the defect was closed with fat and fascia lata and (c) the grafts reinforced with MT flap
Blue arrow: frontal recess; yellow star: defect in cribriform plate; double blue asterisk: fat graft; yellow asterisk: middle turbinate flap

one patient (7.6%) had combined foveal and planar defect. Mean defect size was 3.19±0.72 cm^2.

Graft Materials

Fat was used in all patients with CSF fistula. Septal cartilage was used in 11 of 13 (84.6%) patients. Fascia lata was used in all patients irrespective of etiology.

Flap Harvest

MT flap was successfully harvested in 11 of 13 (84.6%) patients. HB flap was harvested in two patients, in whom the MT flap could not be harvested successfully. Ten of 11 (90.9%) patients with MT flap cover had successful outcome with no evidence of recurrence. The reason for failure in harvesting an MT flap in the two patients was hypotrophied middle turbinate. There was destabilization of MT during the procedure, which lead to unsuccessful attempt. No iatrogenic CSF leak was reported.

One patient had recurrent CSF leak after 12 months. The patient was advised revision surgery but lost to follow up. The primary etiology of that patient was benign intracranial hypertension.

Follow-up and Complications

The average follow-up period of the study cohort was 17.45±5.87 months. No haemorrhagic or non-haemorrhagic complications were reported in the postoperative period.

Discussion

Endonasal endoscopic approaches are preferred for ventral skull base defects associated with CSF leak or meningo-encephaloceles. Multi-layered reconstruction using autologous grafts, flaps and synthetic materials are required for successful outcome (9, 10). Various intranasal and extranasal flaps have been described for this purpose. Pedicled vascular flaps augment and strengthen the grafts, thereby reduce the chances of failure. Commonly used intranasal flaps are the HB flap, the IT flap and the MT flap (1).

HB flap remains the workhorse flap for various ventral skull base reconstructions. The main advantages of this flap are its availability in large quantity and its less demanding surgical technique. It is ideal for larger skull base defects, especially for defects after tumor removal. The disadvantages of this flap are its unavailability in patients with septal perforation and prior nasal surgeries (11, 12). Tamura et al. (5) have demonstrated that inferior turbinate flaps can be effectively used in the reconstruction of sellar and clival defects. However, its utility in cribriform and planar defects requires further research.

MT flap for the reconstruction of skull base defects was first described in cadavers by Prevedello et al (8). They demonstrated the utility of MT flap in cadavers and concluded that it is suitable for medium sized cribriform, foveal and planar defects. According to the literature, the average cross-sectional area of this flap is 5-9 cm^2, which is sufficient to reconstruct medium sized defects (13, 14). Reports also emphasized that preventing

destabilization of the MT while harvesting is critical for success and prevention of CSF leak. Harvesting an MT flap requires expertise, as MT is not a firm structure. Open book technique is the most preferred approach for MT flap harvest. The authors prefer Plester's knife, which is a common instrument used in ear surgeries, to elevate the mucoperiosteum over the MT. The knife is flag shaped and helps in elevation of mucoperiosteum in the medial surface of MT without causing excessive traction.

Identification of the main trunk of SPA before harvesting the flap helps in creating a pedicle up to the posterior attachment of MT to perpendicular plate of palatine bone. It also ensures that the surgeon does not cut the pedicle accidentally. Creating a longer pedicle aids a bigger arc of rotation, thereby reaching to the more anterior parts of cribriform plate. Adequate widening of the maxillary sinus ostium helps in placing the flap temporarily inside the sinus during the surgery.

However, MT flap is difficult to harvest in situations like concha bullosa, paradoxical middle turbinate and hypoplastic turbinate (15). MT flap was unsuccessful in two patients in this study. Both had hypoplastic middle turbinate, which lead to the destabilization of the MT bone. Anatomical deformities can be identified preoperatively by CT scans and nasal endoscopy. Though they are not absolute contraindications for MT flap harvest, surgeon should be aware of such difficult situations and should have an alternative.

Simal Julián et al. (14) have analyzed outcomes of the MT flap in the reconstruction of ventral skull base defects. All the patients in their study were operated on for either pituitary macroadenoma, or arachnoid cyst, or Rathke's cleft cyst. George et al. (16) reported 100% success rate with MT flap reconstruction in their study of 20 patients. All their patients had small to medium sized defects. In our study, we only included patients with medium sized defects. Smaller defects do not require pedicled flap reconstruction while larger defects with tumors require a larger flap like nasoseptal flap. Role of mucosal flaps in medium sized defects is based on the pathology, site of the defect, and the surgeon. In this study, mucosal flap was used in all cases irrespective of etiology, as mucosal flaps help in stability and fixation of grafts along with faster healing of mucous membranes in the surgical area.

Carrabba et al. (17) reported the incidences of recurrent CSF leak and tension pneumocephalus after MT flap reconstruction as 24% and 6%, respectively. However, the results of their study were based on the reconstruction of clival defects. In our study, 10/11 (90.9%) patients had successful outcomes without any notable complications. The results of our study show that MT flaps can be used effectively in cribriform and foveal defects with less morbidity.

The authors emphasize that MT can be a viable option for defects in sphenoethmoidal recess, as it is closer to the defect. Many studies in the literature have reported successful outcomes with MT flaps in sellar and clival defects. However, the authors have no experience on sellar and clival defects. Smaller sample size and retrospective nature of the study makes comparison with control groups difficult. Skull base tumors were not included in the study as the authors do not have much experience in such cases. However, the authors are conducting a study in skull base reconstruction following tumor removal, and the results will be published in the near future. The grafting technique used to reconstruct was not similar leading to lack of standardization in surgical technique. We recommend a prospective study with standard surgical techniques to assess the outcomes.

Conclusion

We conclude that the MT flap is effective in the reconstruction of ventral skull base defects. Appropriate surgical technique is critical for the successful harvest of the flap. Further studies with larger sample sizes are required to analyze its outcomes in various skull base lesions.

Ethics Committee Approval: Ethics committee approval was received for this study from the Sri Ramachandra Institute of Higher Education and Research (Approval Date: February 17, 2020; Approval Number: 23/2020).

Informed Consent: Informed consent was obtained from the patients who participated in this study.

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The Diagnostic Efficacy of MRI in the Evaluation of the Enlarged Vestibular Aqueduct in Children with Hearing Loss

Original Investigation

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Abstract

Objective: The aim of our study is to evaluate the diagnostic effectiveness of magnetic resonance imaging (MRI) compared to computed tomography (CT) in the detection of enlarged vestibular aqueduct (EVA) in childhood.

Methods: One hundred twenty-three children who underwent temporal bone CT and MRI examinations for hearing loss between 2013 and 2020 were evaluated retrospectively. All CT and MRI images were examined by two pediatric radiologists, according to the Valvassori and Cincinnati criteria for EVA. Imaging findings on CT and MRI of the vestibular aqueduct were recorded. Two pediatric radiologists performed the measurements for EVA on CT and MRI. In addition, an otolaryngologist performed the measurements independently. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of MRI compared to CT were calculated to detect EVA. The difference between the measurements on CT and MRI was investigated. The inter-observer agreement was evaluated for measurements.

Results: The mean age of 123 children (65 boys and 58 girls) was 50.18±50.40 months. Two hundred forty-six ears were evaluated in 123 children. On CT images, EVA was present in 28 (11.3%) of 246 ears according to Cincinnati criteria and 27 (10.9%) of 246 ears according to Valvassori criteria, respectively. While sensitivity, specificity, PPD, and NPD rates of MRI were 100%, 99%, 92.8%, and 100%, respectively, for Cincinnati criteria, for Valvassori criteria, they were 100%, 97.3%, 77.7%, and 100%, respectively. According to the visual evaluation performed without using measurement, the enlarged appearance of the vestibular aqueduct was significant for the diagnosis of EVA ($p<0.001$), while the absence of this appearance was significant for the exclusion of EVA ($p<0.001$). There was no significant difference between the measurements on CT and MRI. There was a perfect correlation between the observers for measurements.

Conclusion: MRI can be used as an initial imaging technique in children with suspicion of EVA to reduce radiation exposure.

Keywords: Magnetic resonance imaging, computed tomography, vestibular aqueduct, inner ear, diagnostic imaging, pediatric radiology

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Introduction

Enlarged vestibular aqueduct (EVA) is one of the most frequent congenital inner ear abnormalities in children with sensorineural hearing loss (1). Valvassori and Clemis (2) have described the most commonly used criteria for determining the EVA in 1978. The term EVA refers to a greater diameter than 1.5 millimeters (mm) at the vestibular aqueduct's midpoint. Another definition of EVA, which has been introduced by Boston et al. (3) and called the Cincinnati criteria, is also widely used in daily clinical practice. According to Cincinnati criteria, the EVA diagnosis is confirmed when the diameter of the vestibular aqueduct is greater than 2 mm in the operculum and/or 1 mm in the midpoint on the axial images.

Computed tomography (CT) provides a high spatial resolution allowing accurate measurements of the tiny temporal structures. Short acquisition time, which does not generally require sedation, is another advantage of CT. However, as is known, ionizing radiation is a major disadvantage associated with CT scans, especially in the pediatric age

group. Children have a higher risk of leukemia and brain tumors due to ionizing radiation (4). Given the concern about exposure to ionizing radiation associated with CT scans, magnetic resonance imaging (MRI) has been proposed as an alternative first-line diagnostic tool for some common pathologies in children (5-7). Although CT has been accepted as the gold standard diagnostic tool in detecting inner ear abnormalities according to the previous literature (8), the advancing MRI technology has recently enabled a comprehensive evaluation of inner ear structures (9, 10). High resolution three-dimensional T2-weighted sequences allow visualization of small inner ear structures through exceptional image contrast between cerebrospinal fluid, vessels, and cranial nerves (10, 11).

This study aims to evaluate the diagnostic performance of MRI in detecting EVA in childhood. We aimed to reveal whether MRI would be an efficient first-line diagnostic test to detect EVA and ensure safety by avoiding ionizing radiation exposure in the pediatric age group.

Methods

Patients

The study was approved by the Institutional Review Board of Dokuz Eylül University School of Medicine (Protocol Number: GOA 2020/12-07). Written informed consent was obtained from the legal care-givers of all participants.

We retrospectively reviewed all pediatric patients (age range, 0-18 years) admitted to the Department of Otorhinolaryngology, Dokuz Eylül University School of Medicine, for hearing loss and underwent temporal bone CT and MRI between January 2013 and April 2020. Children diagnosed with unilateral or bilateral hearing loss, who were between 0-18 years old, and underwent temporal bone CT and temporal MRI were eligible. A child presenting with a temporal bone tumor invading the inner ear and 12 children whose radiological images included severe motion artifacts were excluded. Individuals with congenital cochleovestibular abnormalities, syndromic hearing loss, prenatally or postnatally acquired hearing loss were not further excluded because figuring out the EVA's presence or absence by using MRI was our primary purpose.

Main Points

- Magnetic resonance imaging offers high diagnostic performance for the diagnosis of enlarged vestibular aqueduct when using either the Cincinnati or Valvassori criteria.
- An enlarged-appearance of the vestibular aqueduct without using the measurements is a highly suggestive finding for the enlarged vestibular aqueduct. Also, the non-visible vestibular aqueduct's appearance is beneficial to exclude the diagnosis of the enlarged vestibular aqueduct on magnetic resonance imaging.
- We recommend using Magnetic resonance imaging as a first-step imaging technique in children with suspicion of an enlarged vestibular aqueduct to reduce the exposure of ionizing radiation.

Hearing assessment of the patients was carried out by a pure tone audiometer (GN Otometrics Madsen Astera^2, Taastrup, Denmark). The hearing loss was categorized as sensorineural hearing loss (SNHL), conductive hearing loss (CHL), and mixed hearing loss (MHL) for each ear separately, based on the recommendations of the Hearing Committee of the American Academy of Otolaryngology-Head and Neck Surgery (12). Finally, 123 children were enrolled in the study.

CT and MRI Protocol

Temporal bone CT images were obtained using a multi-detector CT scanner (Brilliance 64 Philips; Philips Medical Systems©, Eindhoven, The Netherlands). The field of view (FOV) was adjusted from the arcuate eminence to the mastoid tip. The acquisition parameters were as follows: slice thickness, 0.67 mm; slice interval, 0.33; pitch, 0.348; rotation time, 0.75 second (s); matrix, 768×768; FOV, 14×14 centimeters (cm); collimator, 20×0.625; 120 kilovolts (kV); 150 milliamperes (mA); bone algorithm reconstruction.

Temporal bone MRI images were obtained by a 1.5-Tesla MRI scanner (Gyroscan Achieva, release 8.1; Philips Medical Systems, Best, The Netherlands). In case of necessity, sedation was applied either orally or intravenously. Axial T1-weighted, axial and coronal T2-weighted, and axial T2-balance fast field echo (BFFE) weighted images were used for routine temporal MRI in our department for congenital sensorineural hearing loss. Contrast-enhanced images were also used in patients with acquired hearing loss. The features of imaging procedure were as follows: T1-weighted (time to repetition [TR], 500 milliseconds (ms); time to echo [TE], 15 ms; slice thickness, 3 mm; interslice gap, 0.5 mm; FOV, 20×20 cm; number of excitations [NEX], 3); T2-weighted (TR, 3300 ms; TE, 100 ms; slice thickness, 4 mm; interslice gap, 0.5 mm; FOV, 20×20 cm; NEX, 3); BFFE (TR, 6.8-7.3 ms; TE, 1.4-3.3 ms; slice thickness, 0.6 mm; FOV, 18×18 cm; NEX, 4).

Image Interpretation

Two pediatric radiologists, who have eight and 26 years of clinical experience in pediatric neuroradiology, read the CT and MRI images of 246 temporal bones. Then, the measurements were consulted by a ten-year experienced otorhinolaryngologist.

The radiologists, independent from each other, categorized the vestibular aqueducts' appearances on CT images based on their visual appearance (without any measurements) to correspond one of the enlarged, not enlarged, or suspiciously enlarged type (Figure 1). The midpoint and operculum measurements were performed for the enlarged and suspiciously enlarged types, as previously described (9, 13, 14), while no further measurements were required for the not enlarged types. The midpoint width was measured at the vestibular plane, which corresponds to the horizontal plane that the common dorsal crus arises from the vestibule. The opercular width referred to the maximum perpendicular vestibular aqueduct width at the operculum level. When the measurement met the Valvassori or Cincinnati criteria, the EVA diagnosis of that ear was confirmed.

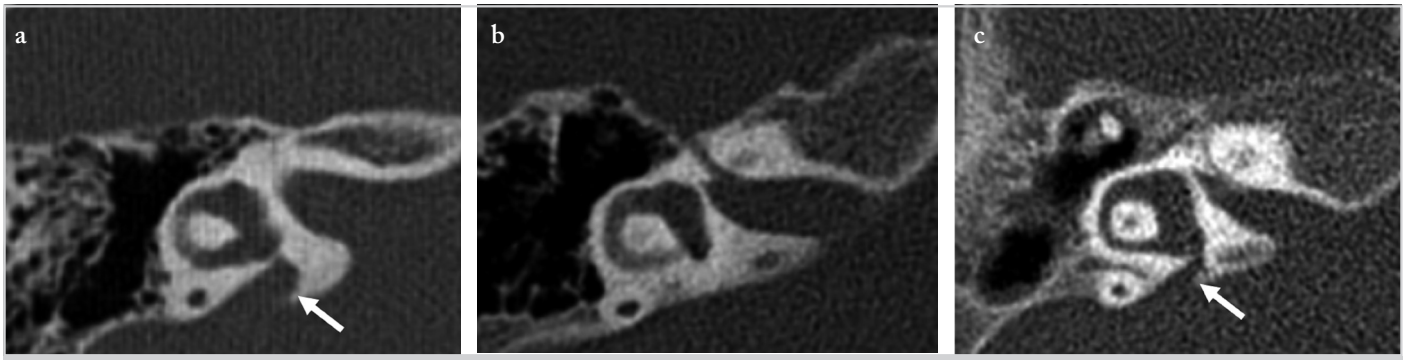

Figure 1. a-c. The classification of the vestibular aqueducts according to the visual analysis on CT scan. (a) The enlarged appearance of the vestibular aqueduct (arrow). (b) The non-enlarged vestibular aqueduct. (c) The vestibular aqueduct with suspicious enlargement (arrow)

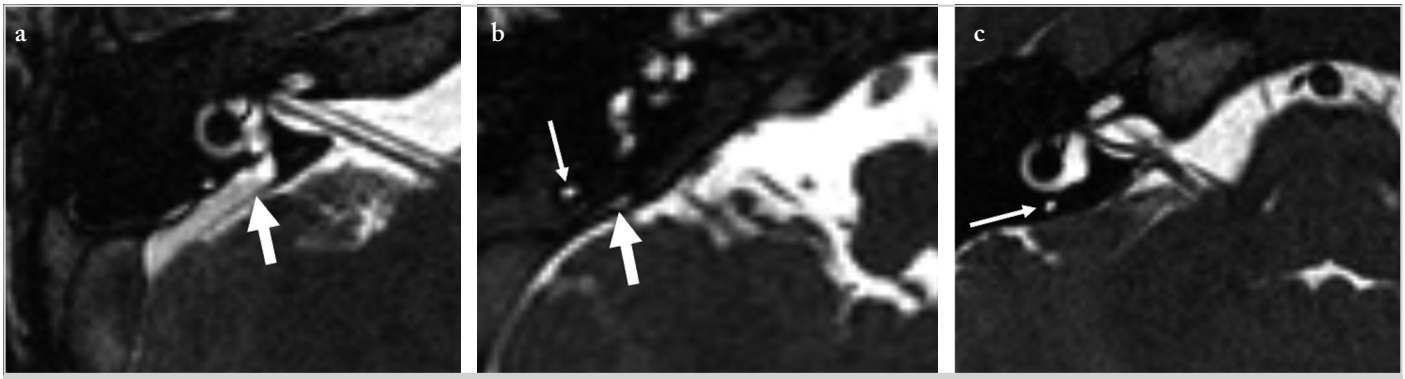

Figure 2. a-c. The classification of the vestibular aqueducts according to the visual analysis on MRI. (a) The vestibular aqueduct with enlarged appearance (arrow). (b) The visible vestibular aqueduct without an enlarged appearance (thick arrow). The posterior semicircular canal (thin arrow). (c) The non-visible vestibular aqueduct. The posterior semicircular canal (arrow)

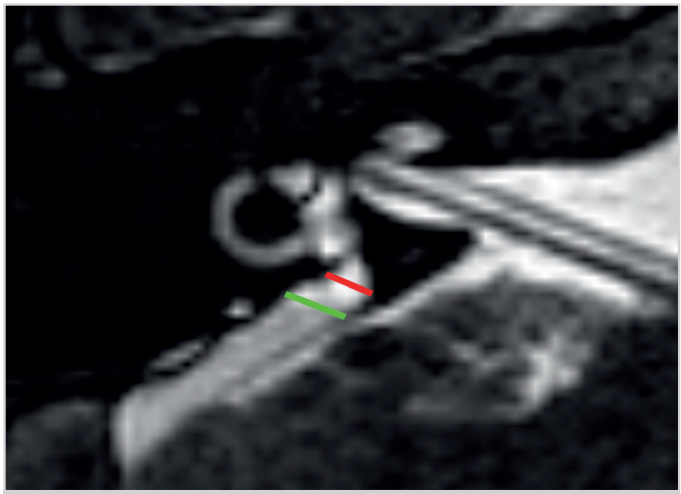

Figure 3. The measurements of the midpoint (red line) and operculum (green line) are demonstrated on the axial MRI image

The radiologists interpreted the MRI images three weeks after the CT evaluation. They classified the MRI findings of the vestibular aqueduct into three groups: the non-visible vestibular aqueduct, the visible vestibular aqueduct without an enlarged appearance, and the vestibular aqueduct with enlarged appearance (Figure 2). If the vestibular aqueduct was not visible, EVA was considered absent. For those ears with visible vestibular aqueducts (with enlargement or without enlargement), the width of vestibular aqueducts was identified by MRI (Figure 3).

The widths of the midpoint and operculum of the vestibular aqueducts were recorded. The ears were classified as EVA group and non-EVA group according to both the Cincinnati and the Valvassori criteria.

Statistical Analysis

Statistical analyses were performed with IBM Statistical Package for the Social Sciences version 22.0 (IBM SPSS Corp.; Armonk, NY, USA). Categorical variables and continuous numerical data were presented as frequency counts and percentages; and mean±standard deviation, respectively. The degree of inter-observer agreement was investigated by the intra-class correlation coefficient. Accordingly, poor, moderate, good, and excellent agreements were defined as the intra-class correlation coefficients to be less than 0.40, 0.41-0.60, 0.61-0.80, and greater than 0.80, respectively. Spearman's correlation coefficient was utilized to assess the correlation between the widths of the midpoint and operculum. The comparison between the EVA measurements obtained by CT and MRI was performed using the Independent Samples t-Test. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of MRI in EVA diagnosis were calculated. Chi-square and Fisher's exact tests were used for evaluating the relationship between the EVA and imaging findings of MRI. A p-value of lesser than 0.05 was considered as statistically significant.

Results

A total of 123 children (65 boys and 58 girls) were enrolled in the study. The mean age was 50.18±50.40 months (range, 3 to 192 months). Thirteen patients had unilateral hearing loss. Among 246 temporal bones in 123 patients, the frequencies of SNHL, CHL, and MHL were found to be 227 (92.2%), 1 (0.4%), and 5 (2%), respectively. Thirteen of 246 ears were presented with normal hearing (5.2%).

Eighteen of 246 vestibular aqueducts were enlarged, 23 of 246 showed a suspicious appearance for enlargement, and 205 of 246 were not enlarged according to the visual analysis on CT scans. When the Cincinnati criteria were followed as the gold standard on CT, 28 (ten of 23 ears showing a suspicious appearance for enlargement and all ears with enlarged-appearance) of 246 (11.3%) ears were included in the EVA group. On MRI, EVA was verified in 26 of those 28 ears (92.9%), which were diagnosed with EVA according to CT scans. The vestibular aqueducts of the remaining two ears with EVA were non-visible on MRI. None of the ears were false-positive for EVA on MRI. MRI had a sensitivity of 100%, a specificity of 99%, a PPV of 92.8%, and an NPV of 100% for detecting the EVA.

When the Valvassori criteria were followed, EVA was confirmed in 27 of 246 (10.9%) ears on CT images. One ear with a suspicious appearance for vestibular aqueduct enlargement on visual assessment was included in the EVA group according to the Cincinnati criteria, while assigned in the non-EVA group according to the Valvassori criteria (the widths of the midpoint and operculum were 1.2 and 3.3 mm, respectively) (Figure 4). Twenty-two of 27 ears (81.5%) with EVA were verified on MRI. The imaging findings of five ears with EVA, which could not be demonstrated on MRI, consisted of four ears with visible vestibular aqueducts without an enlarged appearance and one ear with a non-visible vestibular aqueduct. Another ear with a non-visible aqueduct on MRI, which was mentioned above, was not classified into the EVA group based on the Valvassori criteria. MRI had a sensitivity of 100%, a specificity of 97.3%, a PPV of 77.7%, and an NPV of 100% for detecting the EVA. The diagnostic performance of MRI was shown in Table 1.

The imaging findings of the vestibular aqueduct on MRI were summarized in Table 2. An enlarged appearance of the vestibular aqueduct on MRI (26 of 28 EVA ears (92.9%) according to the Cincinnati criteria and 22 of 27 EVA ears (81.5% according to the Valvassori criteria) was a significant indicator for

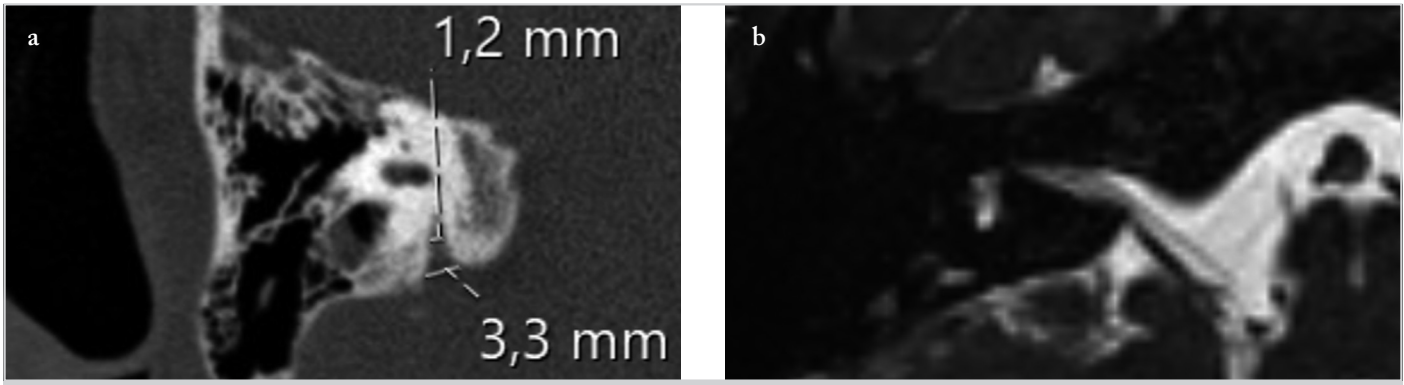

Figure 4. a, b. A patient with an ear included both in EVA and non-EVA groups according to the Cincinnati and Valvassori criteria, respectively. (a) On the CT scan, the midpoint and operculum widths were 1.2 and 3.3 mm, respectively. (b) The vestibular aqueduct was not visible on MRI. Please note that the semicircular canals are dysplastic

Table 1. The diagnostic performances of MRI in detecting EVA*

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
According to the Cincinnati criteria	100 (83.9-1)	99.0 (96.4-99.8)	92.8 (75.0-98.7)	100 (97.8-1)	99.1
According to the Valvassori criteria	100 (80.7-1)	97.3 (94.0-98.9)	77.7 (57.2-90.6)	100 (97.8-1)	97.5

*Numbers in parentheses are 95% confidence intervals (CI)

MRI: magnetic resonance imaging; EVA: enlarged vestibular aqueduct; PPV: positive predictive value; NPV: negative predictive value

Table 2. The appearances of the vestibular aqueducts on MRI

	According to the Cincinnati Criteria			According to the Valvassori Criteria		
	EVA group (n=28)	Non-EVA group (n=218)	p	EVA group (n=27)	Non-EVA group (n=219)	p
Non-visible	2 (7.1%)	193 (88.5%)	<0.001	1 (3.7%)	194 (88.6%)	<0.001
Visible but not enlarged	0 (0%)	25 (11.5%)		4 (14.8%)	25 (11.4%)	
Enlarged	26 (92.9%)	0 (0%)		22 (81.5%)	0 (0%)	

MRI: magnetic resonance imaging; EVA: enlarged vestibular aqueduct

Table 3. Inter-observer reliability

Measurements of the vestibular aqueduct	ICC	95% CI	p
At the midpoint on CT	0.991	0.980-0.996	<0.001
At the midpoint on MRI	0.975	0.946-0.988	<0.001
At the ostium on CT	0.981	0.960-0.991	<0.001
At the ostium on MRI	0.974	0.944-0.988	<0.001

ICC: intra-class correlation coefficient; CI: confidence interval. CT: computed tomography; MRI: magnetic resonance imaging

EVA (p<0.001). The non-visible vestibular aqueduct (193 of 218 non-EVA ears (88.5%) according to the Cincinnati criteria and 194 of 219 non-EVA ears (88.6%) according to the Valvassori criteria) was a statistically significant indicator to exclude the diagnosis of EVA (p<0.001) (Figure 1).

The inter-observer reliability results between the otorhinolaryngologist and radiologists for the measurements of the vestibular aqueduct on CT scan and MRI are summarized in Table 3. Excellent inter-observer agreements were obtained. The values provided by the radiologists represented the mean values. The mean midpoint width was 3.02±1.06 and 2.57±1.20 on CT and MRI, respectively. The mean operculum width was 5.15±1.87 and 4.35±2.06 on CT and MRI, respectively. There were no significant differences regarding the midpoint (p=0.061) and operculum (p=0.053) between CT and MRI. There were excellent correlations between the measurements of the midpoint and operculum on the CT and MRI (p<0.001; Rho=0.826, p<0.001; Rho=0.899, respectively).

Discussion

Currently, there has been no consensus on which initial imaging modality should be performed in children who are clinically suspicious for the presence of EVA. Despite the well-known and widely-used CT-based diagnostic criteria, we investigated the potential diagnostic capability of MRI in EVA due to our concerns about exposure to CT-based ionizing radiation in children. Our results indicated that MRI was quite valid to diagnose EVA with a sensitivity of 100% and a specificity of 97-99%. The NPV values of MRI were 100% for both of the criteria. The non-visible vestibular aqueduct was an indicator to exclude EVA on MRI. Moreover, a vestibular aqueduct with enlarged appearance on MRI was found to be a significant parameter for detecting EVA according to the Cincinnati (92.9%) and Valvassori criteria (81.5%).

Only a few studies have evaluated the diagnostic capability of MRI in comparison to CT to diagnose EVA (9, 15). In 1997, Dahlen et al. (15) reported that 33 of 38 ears (86.8%) were positive for EVA on MRI. However, they suggested that MRI is a complementary imaging tool to CT in the diagnosis of EVA due to its false-positive and false-negative results. A recent study conducted by Connor et al. (9) observed no differences between the vestibular aqueduct measurements using CT and MRI in children with EVA. They defined the diagnostic agreement for CT and MRI to be 93%. They demonstrated that a few false-positive and false-negative cases were present on MRI. We did not find any false-positive findings on MRI. According to our results, the enlarged appearance of the vestibular aqueduct on MRI was correlated with EVA diagnosis, which was confirmed by either the Valvassori or the Cincinnati criteria. Hence, we suggest the use of MRI as a first-step diagnostic tool instead of a CT scan to exclude EVA and to perform a CT scan if required for those cases with high clinical suspicion of EVA in pediatric age. Although MRI has high diagnostic accuracy and NPV according to our results, considering the pediatric age group, we recommend not to underestimate the potential necessity of sedation or anesthetic administration to maintain the stability of positioning during the long acquisition time of MRI, and we highlight this as a limitation.

CT has a high spatial resolution, which means the capability of distinguishing two small, discrete objects (16). In the literature, vestibular aqueducts' measurements showed lower values on MRI than CT, though there were not any statistically significant differences (9, 15). It has been proposed that the lower values on MRI might be related to the challengings of distinguishing between the tip of the thin bony operculum and dura. Besides, a transient enlargement of the fluid space that resulted in a widening of the vestibular aqueduct has also been suggested as another theory to explain these differences (9, 15). Our results were compatible with the literature. Another strength of our study was the reliability of the measurements between two independent assessors. The inter-observer reliability was excellent when the measurements performed on CT and MRI by the otorhinolaryngologist versus pediatric radiologists.

The vestibular aqueduct's normative measurements have been studied in different planes of the temporal bone previously (2, 3, 17-19). Although the classical methods were described in the Valvassori and Cincinnati criteria, the adjacent posterior semicircular canal's width was also used as a standard reference. Also, Juliano et al. (17) revealed that the vestibular aqueduct's normative diameter in the 45° oblique reformat plane was 0.5 mm (0.3-0.9 mm) at the midpoint. Ozgen et al. (18) found that the 45° oblique plane on CT scan was more reliable for measuring the vestibular aqueduct than the axial plane. The 45° oblique plane was not used in this study since reformat images would be useful solely on CT scan, not MRI. Therefore, an optimal comparison between CT and MRI could not be achieved.

EVA can occur either as an isolated abnormality or accompany by other congenital conditions (20). Associated abnormalities should be meticulously clarified, especially in the preoperative assessment of cochlear implant candidates. Many authors investigated the benefit of using preoperative MRI and CT in pediatric cochlear implant candidates (21-24). They concluded that CT was superior to MRI to identify the temporal bone abnormalities, whereas MRI played a critical role when demonstrating cochlear nerve pathologies and accompanied intracranial morbidities. Nevertheless, they also found many overlaps between the two imaging modalities. Trimble et al. (21) suggested a selective use of both imaging modalities within a diagnostic algorithm. Parry et al. (22) suggested the use of MRI in the first-step evaluation in cochlear implant candidates and to continue with the use of CT if required, such as in the case of suspicion for bony abnormalities. Unlike these results, Gleeson et al. (23) demonstrated that the combined use of CT and MRI was not superior to either modality alone.

The exact incidence of EVA in children is still unknown. However, it has been reported to distribute in a wide range from %0.6 to 10% (19, 25-28). The differences regarding the studies may be due to different factors such as the age of the sample size, imaging techniques, and the evaluation methods. Besides, detecting this abnormality has been improved day by day following the advances in imaging technology. Besides, SNHL, which is known to be the most common clinical manifestation in patients with EVA, has become more detectable in the younger age groups due to universal newborn hearing screening programs. In our study, 11% of the 246 temporal bones had EVA. Our study's high incidence rate may be related to our patient cohort, most of which presented with SNHL (227 of 246 ears [92.2%]).

We agree that the relatively small sample size, the retrospective design, and the lack of vestibular assessment are among the limitations of our study. However, we also wish to remind that evaluating vestibular symptoms in the pediatric age group may be extremely challenging.

Conclusion

MRI has high diagnostic accuracy in EVA when using either the Cincinnati or the Valvassori criteria. The non-visible vestibular aqueduct on MRI is a useful marker to exclude EVA. We believe that our results will make valuable contributions to EVA's diagnostic algorithm in otolaryngologists and radiologists' daily clinical practice. Because it does not necessitate the use of ionizing radiation, MRI may offer a safe and effective diagnostic property in diagnosing EVA in children as a first-step diagnostic tool. Further research is also needed to determine the cost-effectiveness and feasibility of implementing MRI on a large scale.

Ethics Committee Approval: Ethics committee approval was received for this study from the Institutional Review Board of Dokuz Eylül University School of Medicine (Protocol Number: GOA 2020/12-07).

Informed Consent: Written informed consent was obtained from the legal care-givers of all patients who participated in this study.

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Functional and Oncological Outcomes of Open Partial Laryngectomy vs. Transoral Laser Surgery in Supraglottic Larynx Cancer

Original Investigation

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Abstract

Objective: The aim of the presented study was to evaluate the outcomes of open partial laryngectomy (OPL) versus transoral laser surgery (TLS) in patients operated on for supraglottic laryngeal carcinoma based on functional parameters (duration of hospitalization, oral nutritional status and duration of transition to oral feeding, weaning status and duration after tracheotomy, and postoperative voice results) and oncological results (overall survival rate, disease-specific survival rate, recurrence, and presence of second primary tumors) in both groups.

Methods: All laryngeal carcinoma patients who had undergone either OPL or TLS in the period from January 2012 to March 2017 in our center and were followed-up at least for 36 months were included in the study. Statistical analyses were carried out using the t-test and the Mann-Whitney U test to compare the means, and the Kaplan-Meier test for survival analysis.

Results: Fifty patients (44 males and 6 females) met the study criteria, of whom 31 had undergone OPL and 19 TLS. Patients that underwent TLS had less tracheotomy needs, needed shorter hospitalization periods, and transitioned to oral feeding earlier, compared to those that underwent OPL. There were no significant differences between the two groups based on oral feeding rates and voice outcomes. The impact of TLS and OPL on organ preservation in supraglottic laryngeal cancer were comparable. For local recurrences, repeated endolaryngeal laser surgeries and adjuvant treatments could be used in the TLS patient group. There were no significant differences between the two groups based on overall survival rate and disease specific survival rate.

Conclusion: Although no significant differences were found in our study between the two surgical procedures in terms of oncological outcomes, TLS appeared to produce better functional outcomes in supraglottic laryngeal carcinoma than OPL.

Keywords: Larynx cancer, laryngectomy, laser therapy, tracheotomy, survival analysis

Introduction

Larynx is an important organ not only for speech but also for swallowing and breathing (1). These three are vital functions, and diseases of the larynx can lead to their impairment, and sometimes, total loss. As a result, most patients diagnosed with laryngeal cancer prefer treatment modalities that provide better functional results over those that provide the best oncological outcomes.

Presently, laryngeal cancers are more often diagnosed at earlier stages thanks to better access to healthcare and increased awareness about laryngeal cancer among patients and doctors. It is important to diagnose laryngeal cancers at an early stage because their treatment success is higher compared to other cancers. Conservative surgical intervention or radiotherapy improves survival rates and provides successful outcomes in preserving the functions (2).

While total laryngectomy is performed since the last quarter of the 19th century, open partial laryngectomy (OPL) is used since the middle of the 20th century with high oncological success (3, 4). Along with the advances in medical technologies, laser has been an important tool for medical practice. Laser surgery was first used in ophthalmology, then in other disciplines, and is successfully used in the treatment of laryngeal cancer since 1972 (5).

The aim of the presented study was to evaluate the oncological and functional outcomes in patients who underwent OPL or transoral laser surgery (TLS) for supraglottic laryngeal cancer at an academic tertiary referral center.

Methods

The study was approved by the institutional ethics committee of Ankara University School of Medicine (Approval Date: January 11, 2016; Approv-

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al Number: 01-12-16) and performed in accordance with the Declaration of Helsinki, using good clinical practice and by observing the regulatory requirements. Informed written consent was obtained from all participants or their legal representative before initiating any procedure.

The study was conducted at an academic tertiary referral center. All laryngeal carcinoma patients who underwent either OPL or TLS from January 2012 to March 2017 at our tertiary university hospital and were followed-up for at least 36 months were included in the study. Patients whose primary treatment was non-surgical, underwent total laryngectomy and radiotherapy, were initially treated for laryngeal cancer in other medical centers and then referred to our clinic, and patients who were followed-up for less than 36 months were excluded.

Detailed anamnesis, general systemic examinations, and otorhinolaryngological examinations of all patients were recorded. Smoking and alcohol consumption habits, as well as type and duration of major complaints were inquired. Videolaryngostroboscopy (VLS) was performed before the operation, and direct laryngoscopy was performed under general anesthesia in patients without a histopathological diagnosis. During direct laryngoscopy, the location of the tumor, its spread, relationship with surrounding tissues, and suitability for transoral laser surgery were evaluated.

At least one neck imaging such as computed tomography (CT), magnetic resonance imaging (MRI) or ultrasonography (USG) was performed preoperatively in all patients diagnosed with supraglottic cancer. All patients were scanned with either thorax CT or Positron Emission Tomography-Computed Tomography (PET/CT) for exclusion of secondary tumors/metastases to lungs.

All patients were informed about the surgical and non-surgical treatment modalities for laryngeal cancer, and detailed information about open surgery and transoral laser surgery were provided to patients who preferred surgical treatment. Temporary or permanent tracheostomy, infection, bleeding, and the possibility of total laryngectomy according to the condition of the tumor were explained to all patients who accepted the surgery, and informed consent forms were obtained from all. Patients planned for TLS were also informed about the possibility of switching, if necessary, to open surgery during the operation, and asked to provide their signed informed consent forms for open surgery.

Main Points

- Transoral laser surgery provided shorter hospitalization times and earlier transitions to oral intake than open partial laryngectomy in supraglottic laryngeal cancer patients.
- There was no significant difference between the two groups based on oral feeding rates and weaning time from tracheotomy.
- Transoral laser surgery and open partial laryngectomy procedures had similar and acceptable oncological success rates.
- Although local recurrences were more frequently observed in the TLS group, this problem could be overcome with the help of repeated laser surgeries and radiotherapy, and a disease-free survival was ensured for patients.

OPL and TLS were determined according their suitability for each patient. This was discussed with each patient. In patients who underwent OPL, supraglottic laryngectomy and selective neck dissection (level 2, 3, 4) were performed in the same session. Patients stayed at the postoperative intensive care unit (ICU) one night after the procedure. In patients who underwent TLS, first supraglottic laryngectomy was performed, and six weeks later, selective neck dissections (level 2, 3, and 4) were carried out in sequential order. TLS procedures were performed using a CO_2 laser device (AcuPulse Duo, Lumenis, Yokneam, Israel) attached to an operation microscope (OPMI Lumera S7, Zeiss, Jena, Germany) with a micromanipulator. Following laryngectomy, biopsies were taken from the surgical margins before finishing the procedure and sent for frozen section analysis. In the post-operative six-week period, laryngectomy specimens were examined by pathologists, and, if necessary, a surgical margin extension procedure was performed under general anesthesia.

After the surgical procedure, functional outcomes, pathology results, follow-up periods, complications, and recurrences were retrospectively evaluated and carefully examined. Functional outcomes included hospitalization period, oral intake, time to oral intake after surgery, tracheotomy status, weaning time from tracheotomy, and voice quality. All frequencies could not be evaluated by the analysis software, and thereby an objective voice analysis could not be carried out because of the low frequency of patients' voices in the postoperative period. To evaluate the voice quality, patients were asked to assess their voice as good, moderate and poor, based on the adequacy and the impact on their daily communication skills. According to the recent TNM Classification of malignant tumors (TNM) system (American Joint Committee on Cancer [AJCC] 2017), clinical and pathological staging was determined following preoperative VLS, radiological examinations, intraoperative findings, and pathology results.

Statistical Analysis

IBM Statistical Package for the Social Sciences for Windows software v20.0 (IBM SPSS Corp.; Armonk, NY, USA) was used for statistical analyses. The OPL and TLS treatment groups were compared using the t test for group means, and the Mann-Whitney U test for median values. Qualitative variables were evaluated with Pearson's chi-square test or Fisher's test. The Kaplan-Meier test was used for survival analysis. P values smaller than 0.05 were considered statistically significant.

Results

Demographic Results

A total of 50 patients (44 men [88%] and 6 women [12%]) with supraglottic laryngeal cancer who met the study criteria were included in the study. Male to female ratio was 7.34 (44/6).

Table 1. Sex, mean age and tumor location of the two treatment groups

	TLS	OPL
Sex		
Male	18	26
Female	1	5
Mean age (years)	60.9	56.6
Tumor location		
Epiglottis	11	19
Band ventricle (false vocal fold)	7	9
Aryepiglottic fold	1	2
Tongue base	0	1

TLS: transoral laser surgery; OPL: open partial laryngectomy

Table 2. Functional outcomes of the two treatment groups for the patients with supraglottic larynx cancer

	TLS	OPL	p
Hospitalization time (days)	9.6	25.7	0.034
Oral feeding ratio (%)	69	71	0.17
Oral feeding duration (days)	2.4	36.6	0.047
Intraoperative tracheotomy ratio (%)	16	100	
Weaning time from tracheotomy (days)	70.5	44.7	0.68

TLS: transoral laser surgery; OPL: open partial laryngectomy

OPL was performed in 31 patients (62%) and TLS in 19 patients (38%). Of those who underwent OPL 26 (83.9%) were male and five (16.1%) were female; and of those who underwent TLS 18 (94.7%) were male and one (5.3%) was female.

The mean age of the patients in the OPL group was 56.6 years (range: 43-83), and the mean age of those in the TLS group was 60.9 years (range: 41-79). There was no significant difference between the mean ages of the two groups. Age distributions were also similar in the two treatment groups.

Hoarseness was the most common complaint of the patients. Thirty-seven patients (74%) consulted the doctor for hoarseness, eight patients (16%) for swallowing difficulty and three patients (6%) for throat pain. One patient (2%) had breath shortness complaint and one patient (2%) presented with a neck mass.

As for patients' histories: 47 (94%) were smokers; and only three (6%) who were diagnosed with laryngeal cancer were non-smokers. While nine patients (18%) reported that they regularly consumed alcohol, others reported that they did not have this habit.

In terms of tumor localization, epiglottis was the leading site. While a majority of the tumors (in 30 patients, 60%) were in the epiglottis, 10 patients (20%) had the tumor in the left band ventricle, six patients (12%) in the right band ventricle, three patients (6%) on the aryepiglottic fold and one patient (2%) on the base of the tongue (Table 1).

Functional Outcomes

The average length of hospital stays after TLS was 9.6±5.6 days (range: 1-22), and 25.7±10.1 days (range: 13-51) after open surgery. The difference was statistically significant (p=0.034).

Nine of the OPL (29%) and six of the TLS patients (31%) were discharged with a long-term feeding tube or percutaneous endoscopic gastrostomy (PEG) due to aspiration in oral feeding. The mean time to oral intake was 36.6±27.7 days (range: 12-120) after open surgery and 2.4±3.0 days (range: 0-9) after TLS. While there was no statistical difference between the two groups in terms of the number of patients who could not switch to oral intake (p=0.17), transition to oral intake was significantly better in the TLS group than in the open surgery group (p=0.047).

Intraoperative tracheotomy was performed in every patient who underwent open surgery. Twenty-three patients (74%) were weaned from tracheotomy in an average of 44.7±46.5 days (range: 14-180). Only three of the TLS patients (16%) underwent intraoperative tracheotomy, and only one (5%) was followed up with permanent tracheotomy. Of the two patients with temporary tracheotomy, tracheotomy was closed on the 39th day in one patient, while the tracheotomy of the other patient was closed on the 102nd postoperative day after the end of the chemoradiotherapy (CRT). There was less need for intraoperative and permanent tracheostomy in the TLS group, but the difference between the weaning times of the two groups was not significant (p=0.68) (Table 2).

Twenty-five patients in the open surgery group were evaluated subjectively in terms of voice. While two patients (8%) defined their voice as poor, 13 patients evaluated as good (52%) and 10 patients (40%) as moderate. In the TLS group, 14 patients (74%) considered their voice quality as good, four patients (21%) as moderate, and one patient (5%) as poor. Since the evaluation was performed subjectively, no statistical analysis was made.

Oncological Outcomes

All patients were evaluated clinically based on their preoperative examinations, imaging, and intraoperative findings (Table 3). Their pathological evaluations, on the other hand, were carried out after completion of the histopathologic examinations (Table 4). Updated AJCC classification of 2017 was used for staging (6).

The average follow-up period after surgery was 66 months (range: 36-99) in patients who underwent OPL and 62 months (range: 38-90) in patients who had TLS. There was no significant difference between the two groups in terms of follow-up periods.

Table 3. Clinical T and N stages and percentages of the patients in the study

Clinical staging	Number of patients (%)
T 1	15 (30)
T 2	31 (62)
T 3	3 (6)
T 4	1 (2)
N 0	42 (84)
N 1	2 (4)
N 2	5 (10)
N 3	1 (2)
Stage	
1	14 (28)
2	25 (50)
3	5 (10)
4	6 (12)
Total	50 (100.0)

Table 4. Pathological T and N stages and percentages of the patients in the study

Pathological staging	Number of patients (%)
T 1	17 (34)
T 2	24 (48)
T 3	5 (10)
T 4	4 (8)
N 0	39 (78)
N 1	5 (10)
N 2	5 (10)
N 3	1(2)
Stage	
1	16 (32)
2	19 (38)
3	4 (8)
4	11 (22)
Total	50 (100.0)

Eight patients (16%) died during the follow-up period. Five had been treated with OPL. Three patients died due to regional neck involvement of tumor, one due to respiratory insufficiency as a result of lung malignancy and one due to cardiac arrest after a myocardial infarction. One OPL patient was admitted to our clinic with shortness of breath in the 15th postoperative month, and total laryngectomy was performed as recurrence was detected. After total laryngectomy, follow-up continued without recurrence in the 41st postoperative month. In the follow-up of patients who underwent OPL, secondary lung malignancy was detected in two patients and thyroid papillary carcinoma was observed in one patient. These three patients were surgically treated. In one patient who underwent OPL, biopsy was taken from a mass in the submental area in the 57th postoperative month. This turned out to be squamous cell carcinoma. Surgery was recommended to the patient, but the patient wanted to have radiotherapy and was referred to the radiation oncology department. Overall, patients treated with OPL had a five-year survival rate of 83.9% and a five-year disease-free survival rate of 80.6%.

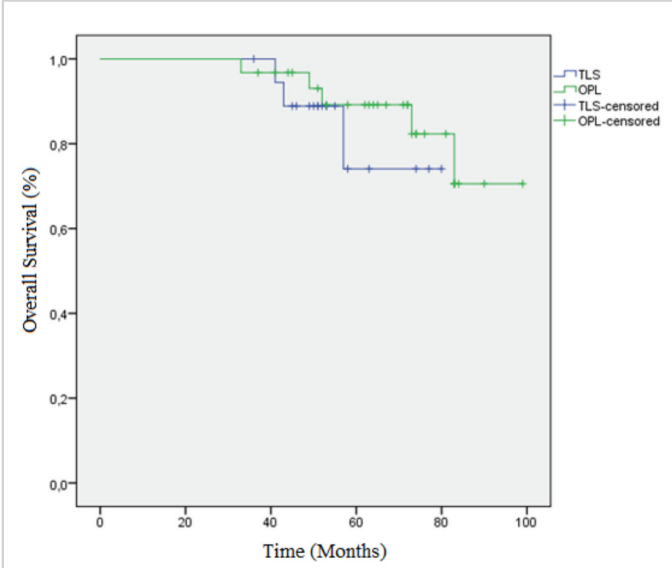

Figure 1. Overall survival rate for the TLS and OPL groups
TLS: transoral laser surgery; OPL: open partial laryngectomy

Three patients in the TLS group died during the follow-up period. Two patients died due to regional recurrence of the tumor and one patient due to hepatic failure after chronic viral hepatitis. Local recurrence was detected in the control examination of five patients. These recurrences were detected in the 14th, 18th, 24th, 24th and 30th postoperative months, respectively. While four of these patients were treated with TLS again, one patient was referred to radiation oncology. Based on the most recent follow-ups, no local or regional progression was observed in the patients. The patients treated with TLS had a five-year survival rate of 84.2% and five-year disease-free survival rate of 79% (Figure 1).

Discussion

Laryngeal cancer is the second most common cancer in the head and neck region after skin cancer (7). In Turkey, laryngeal cancer is the eighth among the top ten most common cancers in men (8). Therefore, it is considered a major public health problem.

The treatment of laryngeal cancer has reached its present state by evolving through different modalities. Theodor Billroth was the first to describe total laryngectomy in 1873 (3). Radiother-

apy started to be used for treatment in the late 1920s. Surgery modalities evolved from total laryngectomy to larynx preservation surgery. Suarez defined supraglottic horizontal laryngectomy (SHL) as a two-step surgery in 1944, which was modified to its present version in 1960 (4). In 1975, Strong (5) reported the results of the first patients treated with laser surgery in Canada. Vaughan et al. (9) reported the first supraglottic laryngectomy with laser in 1978. The FDA approved transoral robotic surgery (TORS) for laryngeal cancer in 2009 (10).

TLS has become a reliable treatment option for supraglottic cancer in the recent years. Today, TLS represents a less invasive protocol that allows tumors to be removed with limited sacrifice of the normal tissue and by preserving the organ function (11). Functional outcomes of TLS are generally considered better than open surgery, and in many cases, they are comparable with radiotherapy and robotic surgery (12, 13). Other advantages of TLS include low morbidity and mortality, less need for tracheotomy and shorter duration of hospitalization (11-13). Furthermore, TLS has repeatedly demonstrated cure rates comparable to those of open surgery or primary radiotherapy in supraglottic cancer (11-13). Although it was previously common to believe that TLS was only an appropriate treatment in early stage (T1, T2) glottic and supraglottic cancers, the results shown by Ambrosch et al. (14) and Mannelli et al. (15) suggested that TLS is also a competent surgery in advanced stage (T3, T4) cancers.

The mean hospitalization time was 9.6 days after TLS and 25.7 days after open surgery in the present study. Kayhan et al. (16) performed TORS on 13 patients with supraglottic cancer and reported a mean hospitalization period of 15.4 days.

In the presented study, nine (29%) OPL and six (31%) TLS patients were discharged with long-term feeding tube or PEG due to aspiration in oral feeding. The mean duration of transition to oral intake was 36.6 days in open surgery and 2.4 days in TLS. Ambrosch et al. (14) reported that only 4% of their patients needed feeding tube or PEG one year after the operation. In their review study, van der Woerd et al. (17) evaluated a total of 640 supraglottic cancer patients in 10 papers, 320 of whom underwent surgery. For the management of aspiration, they reported a permanent tracheostomy or total laryngectomy rate of 2.6% and a permanent gastrostomy rate of 5.3%. In our study swallowing rate at the time of discharge was somewhat lower compared to other studies. However, as a result of swallowing rehabilitation and patient adaptation, the patients did not need total laryngectomy or permanent tracheostomy for the purposes of aspiration control.

In the presented study, intraoperative tracheotomy was performed in all patients who underwent open surgery, and 23 patients (74%) were decannulated at 44.7 days on the average. Only three (16%) of the TLS patients underwent intraoperative tracheotomy, and only one patient (5%) was followed up with permanent tracheostomy. In a study involving 91 patients evaluated over a period of ten years, Ambrosch et al. (14) reported that 13% of the patients required tracheotomy and 74% needed it in the early postoperative period. Estomba et al. (18) compared TLS and SHL groups, and reported that TLS patients required shorter hospitalization periods, faster decannulation times, and had less need for tracheotomy. Thus, the findings in our study are consistent with those of Estomba et al. (18).

Since vocal cords are preserved during organ protective surgeries in supraglottic cancers, voice quality does not change as much as it does in glottic tumors. The removal of false cords or arytenoids in expanded cases could considerably change the voice quality. Topaloğlu et al. (19) found a significant decrease in the maximum phonation time and the fundamental frequency of patients who underwent OPL compared to the control group. They did not, however, observe a significant difference in perceptual and subjective analysis. Roh et al. (20) stated that vocal functions, including the voice handicap index (VHI), the grade, roughness, breathiness, asthenia, strain (GRBAS) scale, and acoustic and aerodynamic parameters did not change significantly after TLS in supraglottic cancer. Oridate et al. (21) compared the voice related quality of life (VRQOL), VHI-10, and GRBAS scores of patients with T2 N0 supraglottic cancer against those of patients with T1a, T1b, and T2 N0 glottic cancers, and found no significant differences in functional outcomes. Since some of our patients continued their follow-up in other centers after five years, perceptual voice evaluations were not carried out on the phone, and only subjective analysis was performed in our study. Re-evaluation of the effects of patients' voices on their daily lives using surveys such as VRQOL and VHI would increase the accuracy of subjective analyses.

The clinical staging of patients was made based on preoperative examinations, imaging methods and intraoperative findings, while pathological staging was made based on the pathological examination of the larynx and neck dissection materials after surgical excision. In our study, the most important reason why advanced-stage patients were found to have such higher frequencies was deemed to be due to the classification of extracapsular involvement as N3b in the 2017 update of AJCC, and also the presence of lymph nodes in the bilateral neck even in the early stage of supraglottic tumors (6).

One of the most important oncological problems encountered during partial laryngectomy is the presence of tumors at the surgical margins. Surgical margin positivity results in higher recurrence rates, decreased local control, disease-specific survival, and lower overall survival rate. Therefore, it is recommended to take biopsies from the surgical margins for intraoperative frozen section analysis. Fang et al. (22) reported that cases with positive surgical margins mostly showed early local recurrence and poor prognosis in early stage glottic cancers. Similarly, Nakayama et al. (23) showed that positive surgical margins in open surgery led to early recurrence and increased mortality rates in 61 supracricoid laryngectomy cases.

In the presented study, the intraoperative frozen section analysis was performed in all TLS patients, and surgical margins were

expanded in case of positive results. Nevertheless, postoperative positivity was detected in five patients in permanent section analysis, and local recurrence was observed during follow-up. Four of the recurrent tumors were re-excised with TLS and the other patient was treated with RT.

One of the most important factors determining survival in supraglottic cancers is the positivity of lymph nodes at the neck. Many studies confirmed that the probability of bilateral lymph node metastasis is high in supraglottic cancers. Ma et al. (24) found a total of 28.1% metastasis risk in clinical N0 necks, and this risk was 15.4% in T2, 32.5% in T3, and 35.7% in T4. Yılmaz et al. (25) stated that the contralateral neck metastasis rate was 16% and the occult metastasis rate was 28% in a retrospective cohort study in Turkey. It was stated that whether the region where the tumor originates is far from or close to the epiglottic midline does not affect the metastasis rates. In contrast to these studies, Ferlito et al. (26) reported that only 1.6% of the supraglottic cancers had an involvement at level 2B and 3.4% of them had a lymph node at level 4 in 272 clinical N0 patients. They suggested that the dissection of levels 2A and 3 would be an adequate treatment. They also reported that bilateral neck dissection should be performed only in centrally located or bilateral tumors and that it would be appropriate to evaluate the other side of the neck in other situations.

In our study, selective neck dissections including levels 2, 3, 4 were performed bilaterally in 18 patients and unilaterally in 13 patients. In three OPL patients who had metastatic lymph nodes, the contralateral neck was operated in a separate session. No pathological lymph nodes were found in other ten patients. No tumors were detected in the contralateral necks of the 10 patients during follow-up. Of the 19 patients who underwent TLS, 12 had bilateral and seven had unilateral neck dissection. The contralateral neck was operated on in one patient due to a metastatic lymph node. No tumor was detected in the other side of the neck in the six patients during follow-up.

Ambrosch et al. (14) observed locoregional recurrence in 15.4% of their patients that underwent TLS. Five-year local control and five-year survival rates were 72% and 63%, respectively. Karatzanis et al. (27) reported that overall five-year disease specific survival was 81.9% and local control was 90.8% in their series. While disease specific survival was 79.4% in T1 cases and 82.9% in T2 cases, local control was 87.0% in T1 cases and 92.3% in T2 cases. Karabulut et al. (28) found an overall survival rate of 88% in the TORS group and 95% in the OPL group. The authors reported the disease specific survival rate as 94% in the robotic surgery group and 95% in the open surgery group.

In our study, five patients in the OPL group died of various reasons. Patients had 83.9% overall survival and 80.6% disease-free survival rates. During the follow-up of the patients in the TLS group, local recurrence was observed in five patients. These recurrences were successfully treated with repeated laser surgery (four patients) and radiotherapy (one patient). Three patients in the TLS group died of various reasons. No local or regional disease progression or recurrence was observed in the most recent follow-ups, and the overall survival rate was 84.2%, and disease-free survival rate was 79%.

Conclusion

The presented study showed that supraglottic cancer patients treated with TLS had shorter hospitalization times, earlier transition to oral intake, and less need for tracheotomy compared to the patients who underwent OPL. They also had better subjective voice quality outcomes. Even though local recurrences were more frequently observed in TLS compared to OPL, it was possible to protect the larynx and to ensure disease-free survival with the use of repeated laser surgeries and radiotherapy.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ankara University School of Medicine (Approval Date: January 11, 2016; Approval Number: 01-12-16)

Informed Consent: Informed consent was obtained from patients or their legal representatives of the patients who participated in this study.

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Complications of Acute and Chronic Otitis Media in a Tertiary Referral Center in Nepal

Original Investigation

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Abstract

Objective: The aim of this study was to report the incidence of complications in otitis media and to determine the frequencies of various extracranial and intracranial complications at a tertiary care hospital.

Methods: We retrospectively reviewed the clinical records of patients of all ages and genders who were treated in a tertiary care hospital in Nepal from May 2015 to May 2020 for complications of acute and chronic otitis media. The complications were broadly classified as extracranial and intracranial. The details of patient profiles, histories, examination findings, investigations and treatments were reviewed from the charts.

Results: The mean age of 164 patients with complications of otitis media was 47.44±18.58 years. There were 79 (48.2%) male and 85 (51.8%) female patients. The overall incidence of otitis media complications was 0.78%. The incidences of the complications from acute otitis media, chronic otitis media without cholesteatoma, and chronic otitis media with cholesteatoma were 0.5%, 0.06% and 5.6%, respectively. Extracranial complications, intracranial complications and combined extracranial and intracranial complications were seen in 80%, 11% and 9% of the patients, respectively. The most common extracranial and intracranial complications were subperiosteal abscesses and brain abscesses, respectively. There was one mortality due to complication.

Conclusion: The incidences of complications and mortality from otitis media have declined with the availability of suitable antibiotics, improved imaging, and multidisciplinary management. Antibiotic resistance and masking of signs and symptoms, however, could pose challenges in the future.

Keywords: Otitis media, middle ear, infection, cholesteatoma, complications

Introduction

Otitis media is the inflammation of the mucoperiosteal lining of the tympanomastoid compartment. The term complication denotes the spread of the infection beyond the mucosal lining of the middle ear cleft (1). Complications of otitis media could be life-threatening, with significant morbidity and mortality.

The complications of otitis media have been classified as intracranial and extracranial (2). They can occur secondary to acute or chronic otitis media with or without cholesteatoma. The prevalence rates of extracranial and intracranial complications are reported to range from 0.69% to 5%, and the rate of mortality from intracranial complications as 8% (2).

Complications of otitis media are a common problem in developing countries (3). The factors responsible for such complications in developing countries could be poverty, lack of education, unavailability of healthcare facilities and ignorance about aural symptoms. In developed countries, however, complications can be caused by antibiotic resistance, masking of symptoms by antibiotics and change in the virulence of causative organisms (4).

The purpose of this study was to report the incidence of complications of otitis media and to determine the frequencies of various extracranial and intracranial complications at a tertiary care hospital.

Methods

A retrospective study was conducted in the department of Otorhinolaryngology of Tribhuvan University Teaching Hospital, Nepal from May 2015 to May 2020. During this study period, 20,797 patients were diagnosed with acute and chronic otitis media. Out of the 20,797 patients, 164 were diagnosed with a complication and their charts were retrospectively reviewed. Ethical approval was obtained on 7th January 2020 from the Institutional Review Committee of Institute of Medicine, Tribhuvan University with protocol number of 278(6-11)E2 076/077. The study was conducted as per the ethical principles described by the Declaration of Helsinki. Informed consent was obtained from all patients.

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Patients of all age groups and genders with a complication of otitis media were included in the study. Complications from acute otitis media were identified in 34 patients, complications from chronic otitis media with cholesteatoma were identified in 123 patients, and complications from chronic otitis media without cholesteatoma were observed in seven patients. The details of patient profiles, histories, examination findings, investigations and treatments were reviewed from the charts. We used Microsoft Office Excel (Microsoft Corp.; Redmond, WA, USA) for data recording and analysis.

The complications of otitis media were classified as extracranial and intracranial. Extracranial complications were mastoiditis, mastoid abscess, mastoid fistula, Bezold's abscess, Luc's abscess, zygomatic abscess, facial nerve paralysis, labyrinthitis and labyrinthine fistula. Intracranial complications were meningitis, brain abscess, extradural abscess, subdural abscess, lateral sinus thrombophlebitis and otitic hydrocephalus.

Results

During the five-year study period, 164 patients were diagnosed with complications of otitis media, of whom 79 (48.2%) were male and 85 (51.8%) were female. The incidence of complications from otitis media was 0.78%. The incidences of complications from different types of otitis media are shown in Table 1.

The age of the patients with complications ranged from seven months to 89 years, with a mean age of 47.44±18.58 years. The mean age of patients with complications from acute otitis media was 23.76±19.68 years. Complications of otitis media were more common in young patients (0 to 20 years) as shown in Figure 1. Similarly, acute otitis media complications were more common in the younger age group (0 to 10 years) as shown in Figure 2. The distribution of extracranial and intracranial complications according to age groups are shown in Tables 2 and 3, respectively.

Among the 164 patients, 155 extracranial complications and 27 intracranial complications were identified. Fifteen out of 164 patients (9%) had more than two complications. The most common co-existing complications were facial palsy and acute

Main Points

- The incidence of complications of acute and chronic otitis media was found to be 0.78%.
- The incidence of complications from acute otitis media has declined with antibiotic use in comparison to the incidence of complications from chronic otitis media.
- The highest incidence of complications was seen in patients aged younger than 20 years.
- The incidence of intracranial complications has declined in comparison to that of extracranial complications.
- Clinicians should be vigilant about the possibility of multiple complications in a single patient.

Table 1. Incidences of complications in different types of otitis media

Type of otitis media	Number of patients with otitis media	Number of patients with complication	Incidence of complication (%)
AOM	6,749	34	0.5
COM with cholesteatoma	2,189	123	5.6
COM without cholesteatoma	11,859	7	0.06

AOM: Acute otitis media; COM: Chronic otitis media

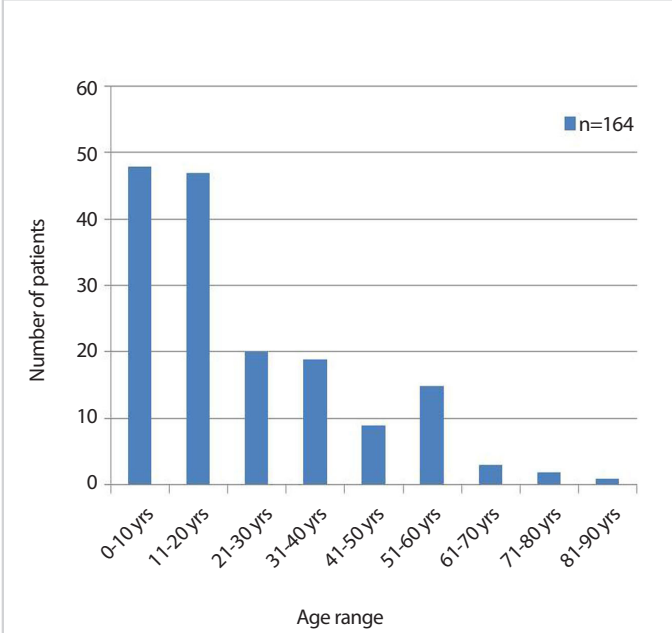

Figure 1. Age distribution of patients by complication (n=164)

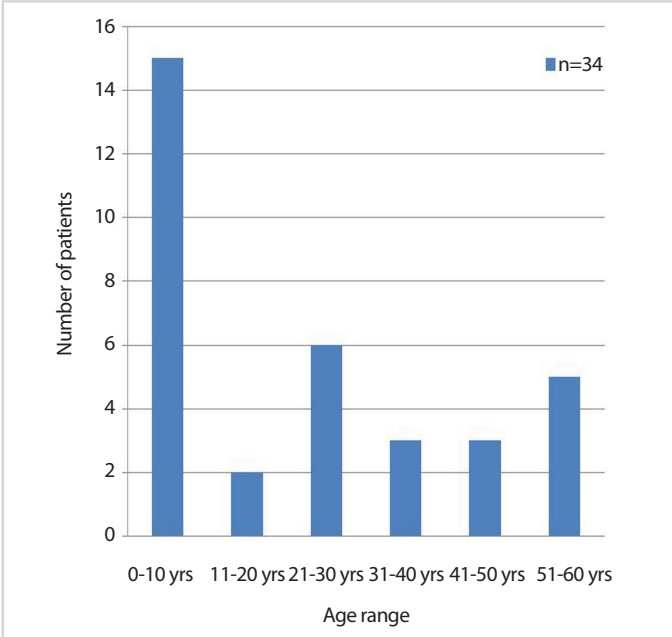

Figure 2. Age distribution of patients by complications from acute otitis media (n=34)

Table 2. Distribution of extracranial complications according to age groups (n=155)

Extracranial complications	0-10 yrs	11-20 yrs	21-30 yrs	31-40 yrs	41-50 yrs	51-60 yrs	61-70 yrs	71-80 yrs	81-90 yrs	Total
Mastoiditis	13	9	5	2	2	4	1	0	0	36 (23.2%)
Subperiosteal abscess	18	14	1	3	2	2	0	0	0	40 (25.8%)
Mastoid fistula	3	2	5	3	1	0	0	0	0	14 (9%)
Facial palsy	7	5	5	6	4	4	1	2	1	35 (22.5%)
Labyrinthitis	1	2	4	7	1	5	0	0	0	20 (13%)
Labyrinthine fistula	1	5	1	2	0	1	0	0	0	10 (6.5%)

yrs: years

Table 3. Distribution of intracranial complications according to age groups (n=27)

Intracranial complications	0-10 yrs	11-20 yrs	21-30 yrs	31-40 yrs	41-50 yrs	51-60 yrs	61-70 yrs	71-80 yrs	81-90 yrs	Total
Meningitis	1	4	1	0	0	1	1	0	0	8 (29.6%)
Brain abscess	3	8	2	0	0	0	0	0	0	13 (48.1%)
Lateral sinus thrombophlebitis	1	0	1	0	0	1	0	0	0	3 (11.2%)
Extradural abscess	2	0	0	0	0	0	0	0	0	2 (7.4%)
Subdural abscess	1	0	0	0	0	0	0	0	0	1 (3.7%)

yrs: years

Table 4. Distribution of extracranial complications by types of otitis media (n=155)

Extracranial complication	Acute otitis media	Chronic otitis media (without cholesteatoma)	Chronic otitis media (with cholesteatoma)	Total
Mastoiditis	18	3	15	36 (23.2%)
Mastoid abscess	2	0	34	36 (23.2%)
Bezold's abscess	0	0	2	2 (1.3%)
Luc's abscess	1	0	0	1 (0.6%)
Zygomatic abscess	0	0	1	1 (0.6%)
Mastoid fistula	0	0	14	14 (9%)
Labyrinthitis	5	1	14	20 (13%)
Labyrinthine fistula	0	0	10	10 (6.5%)
Facial palsy	11	4	20	35 (22.6%)

mastoiditis. However, one patient had four complications together including mastoiditis, meningitis, temporal lobe abscess and lateral sinus thrombophlebitis.

The most common extracranial complication was subperiosteal abscess, followed by mastoiditis and facial palsy. There were 36 cases of mastoid abscess, two cases of Bezold's abscess and one case each of Luc's abscess and zygomatic abscess (Table 4).

All complications secondary to acute otitis media and chronic otitis media without cholesteatoma were extracranial only. Three out of 34 patients with complication from acute otitis media had multiple complications (one had facial palsy and labyrinthitis, and two had facial palsy and mastoiditis). Two of these patients had diabetes mellitus as a comorbidity. One of the seven patients with complication from chronic otitis media without cholesteatoma had two co-existing complications and they were facial palsy and mastoiditis (Table 4).

All 27 intracranial complications were from chronic otitis media with cholesteatoma. Brain abscess was the most common intracranial complication. Eight patients had brain abscess in

Table 5. Distribution of intracranial complications (n=27)

Type of intracranial complication	Frequency of complication (%)
Meningitis	8 (29.6)
Temporal lobe abscess	8 (29.6)
Cerebellar abscess	4 (14.8)
Multifocal brain abscess	1 (3.7)
Lateral sinus thrombophlebitis	3 (11.2)
Extradural abscess	2 (7.4)
Subdural abscess	1 (3.7)

the temporal lobe, four had in the cerebellum, and one had multifocal brain abscess (Table 5). All three patients with lateral sinus thrombophlebitis had multiple complications (one had facial palsy, one had cerebellar abscess, and one had meningitis, mastoiditis, and temporal lobe abscess).

Of the 164 patients with complication, there was one mortality (0.6%). The case was a 51-year old male with chronic otitis media with cholesteatoma. He was a known case of diabetes mellitus with stage four chronic kidney disease on dialysis. He had grade three facial palsy with lateral sinus thrombophlebitis. The patient expired on third post-operative day following canal wall down mastoidectomy.

Discussion

Complications of otitis media can lead to various morbidities and sometimes prove lethal. In the pre-antibiotic era, the mortality from complications of otitis media was reported to be as high as 80%. Survival rates were reported to improve up to 50% with the introduction of sulfonamides, and further to 80% with the introduction of penicillin (5). The incidence of intracranial complications of otitis media was reported to decline from 2.3% to 0.04% after the use of antibiotics (6). However, complications from otitis media continue to be a problem in developing countries like Nepal.

This study was conducted in Tribhuvan University Teaching Hospital, which is one of the oldest and busiest tertiary referral centers in Nepal's capital Kathmandu. The hospital also has the highest bed capacity in the country. Therefore, this study intends to be able to shed light on the changing trends of the complications in the twenty-first century in a developing country, Nepal.

A study by Kangsanarak et al. (7) in Thailand found the prevalence of complications from otitis media to be 0.69%. Similarly, in our study, we found this rate to be 0.78%. However, this rate is still high compared to that from developed countries. Samuel et al. (8) found the incidence of extracranial complications to be 0.13%, and Palva et al. (9) reported the incidence of intracranial complications to be 0.04%. In developed countries, rarity of complications limits the experience of the otologist (1).

Before the advent of antibiotics, 52% of the complications were secondary to acute otitis media. With the use of suitable antibiotics, however, complications encountered today are mostly from chronic otitis media (1). In our study, the incidence of complications from acute otitis media was found to be 0.5%, while the incidence of complications from chronic otitis media with cholesteatoma was found to be 5.6%. This difference between the rates of complications from acute and chronic otitis media may be due to the use of antibiotics and the routine vaccination against *Haemophilus influenza* and *Streptococcus pneumoniae*. Chronic otitis media without cholesteatoma is referred to as the safer type of otitis media, but complications may nevertheless occur. Complications in non-cholesteatomatous otitis media usually occur in neglected cases of tubotympanic disease. The incidence of complications in chronic otitis media without cholesteatoma in this study was 0.06%.

The complications of acute and chronic otitis media were highest in the population under 20 years of age (48.28%). Also, 50% of the complications from acute otitis media were seen in patients aged younger than 20 years. This finding of our study is comparable to that reported by Osma et al. (6), where 58% of patients with complication were under 20 years of age. In our study, 74% of intracranial complications were seen in patients under 20 years of age. Samuel et al. (8) reported 74% of intracranial complications occurring in children and young adults in their study. Complications are more commonly seen in children than in adults given the increased frequency of otitis media in children due to immature Eustachian tube, low immunity, the aggressive nature of paediatric cholesteatoma, well–pneumatized paediatric temporal bone where spread of cholesteatoma becomes easy, and greater inflammatory markers in paediatric cholesteatoma (10).

In a study by Singh and Maharaj (5) with 268 patients in 1993, 32% had extracranial complications, 56% had intracranial complications, and 12% had combined extracranial and intracranial complications. This report contrasts with our study where we found 131 (80%) patients with extracranial complications, 18 (11%) with intracranial complications, and 15 (9%) with multiple complications. In 2011, Wu et al. (11) reported that extracranial complications had gradually increased, whereas intracranial complications had gradually decreased during their 22-year study. The decrease in intracranial complications may be due to the early administration of higher generation antibiotics, the widespread use of high-esolution imaging, and the improvement in microsurgical techniques.

The clinician should be vigilant about the possibility of more than a single complication in patients. Mostafa et al. (12) reported two concurrent complications in 54%, and three or more concurrent complications in 44.7% of their 422 patients. Wu et al. (11) had multiple complications in 10% of their patients, which is a finding comparable to that found in our study. Facial palsy was the most common concurrent complication in our

study. Thorough history taking and detailed clinical examination are mandatory in all patients, to avoid missing out on multiple complications. Sometimes the use of antibiotics can mask the signs and symptoms of complications. Magnetic resonance imaging of the brain is mandatory in addition to high-resolution computed tomography (HRCT) of the temporal bone and should be performed early if the clinician suspects intracranial complication since early intervention reduces morbidity and mortality.

In our study, subperiosteal abscess was the most common extracranial complication, which is comparable to the reports of Osma et al. (6) and Rupa and Raman (13). This tends to vary in other studies, e.g., facial palsy and labyrinthitis were reported as the most common extracranial complications by Kangsanarak et al. (7) and Wu et al. (11). The most common intracranial complication in our study was brain abscess, which is similar to the other reports (6, 11, 13) The most common sites of brain abscess were the temporal lobe, followed by the cerebellum. Sometimes multifocal brain abscess may occur. Kangsanarak et al. (7) reported meningitis and Mostafa et al. (12) reported lateral sinus thrombophlebitis to be the most common intracranial complications.

The complications in relation to mastoid could range from the stage of mastoiditis, subperiosteal abscess formation to mastoid fistula formation. In our study, most of the patients with chronic otitis media with cholesteatoma presented in the stage of subperiosteal abscess; however, patients presenting in the stage of mastoiditis were also common. All 14 patients presenting with mastoid fistula were suffering from chronic otitis media with cholesteatoma and had been unaware of their ear discharge for a long time. In our study, mastoiditis was the most common extracranial complication of acute otitis media, followed by facial palsy and labyrinthitis. It is important to note that 6% to 17% of the patients diagnosed as acute mastoiditis may develop intracranial complications (14). Therefore, early management of a mastoid related complication is essential.

Facial nerve palsy was the second most common complication from chronic otitis media and acute otitis media in our study. All patients in our study had incomplete (grade 3 to 4) facial palsy. The frequency of facial paralysis in different studies range from 0.16% to 2.62% (2). A study performed by Smith and Danner (15) reported that facial palsy in children due to acute otitis media is incomplete, occurs abruptly and has good recovery, whereas facial palsy due to chronic otitis media occurs slowly and has worse prognosis. With the use of antibiotics, the episodes of acute otitis media have declined and so has facial palsy. 80% of patients with facial palsy from acute otitis media recover with intravenous antibiotics and ventilation tube insertion (14). The remainder of patients require cortical mastoidectomy. Facial nerve decompression is usually not advocated in facial palsy from acute otitis media, and the role of corticosteroids seems controversial. The treatment of facial palsy from chronic otitis media is always surgical and should be done promptly to get good recovery (2). The role of facial nerve decompression is controversial, as some groups advocate routine decompression, while other groups advocate that only removal of the disease is sufficient.

Baysal et al. (16) reported the incidence of labyrinthitis to range from 12.8% to 34%. Labyrinthitis was the third most common extracranial complication from acute and chronic otitis media in our study. Patients with labyrinthitis from chronic otitis media with cholesteatoma were treated with intravenous antibiotics, labyrinthine sedatives, and canal wall down mastoidectomy, while surgery was not performed in patients with labyrinthitis from acute otitis media and chronic otitis media without cholesteatoma.

In our study, all labyrinthine fistula cases were caused by chronic otitis media with cholesteatoma, and fistula was seen in the lateral semicircular canal. The incidence of labyrinthine fistulae is 4% to 13% (2). The sensitivity of HRCT in detecting a fistula is 57% to 60% (15). All patients with labyrinthine fistula underwent canal wall down mastoidectomy with removal of the disease overlying the fistula, and repair with temporalis muscle and fascia. The removal of the disease from the semicircular canal should be done cautiously because of the risk of causing sensorineural hearing loss (15).

Brain abscess, which is a serious complication, was the most common intracranial complication in our study. The commonest site of brain abscess was the temporal lobe, followed by the cerebellum. The rate of mortalities from brain abscess was reported by Kangsanarak et al. (7) as 33% and by Osma et al. (6) as 20%. There was no mortality in our study from brain abscess. A multidisciplinary team comprising an otorhinolaryngologist, a neurosurgeon, a critical care physician, an anaesthesiologist, a radiologist and an ophthalmologist is required for the proper management of such a case. Previously, mastoid exploration was recommended to be delayed until the patient recovers after brain abscess drainage. The current recommendation, however, is to perform mastoidectomy in the same session as the brain abscess drainage if the patient can tolerate general anaesthesia (15).

Osma et al. (6), Kangsanarak et al. (7), Dubey and Larawin (17), and Lin et al. (18) reported meningitis to be the most common intracranial complication. In our study, meningitis was the second most common intracranial complication. The mortality rate of meningitis in the pre-antibiotic era was 35% and declined to 5% with the use of antibiotics (15). Ibrahim et al. (19) reported the incidence of meningitis from acute otitis media as 13%, and from chronic otitis media as 3%. Early treatment is necessary to reduce mortality and its sequelae. Surgical intervention is recommended after the patient improves with intravenous antibiotics.

Lateral sinus thrombosis comprises 17% to 19% of the intracranial complications (15). High index of suspicion is required, because nowadays the previously described classical clinical presentation is rare due to the use of antibiotics. Magnetic resonance venography should be done to see the patency of the venous sinuses. There were three cases of lateral sinus thrombosis from chronic otitis media with cholesteatoma in our study and all of them coexisted with other complications such as facial palsy, cerebellar abscess and meningitis, mastoiditis, and temporal lobe abscess. There was one mortality in our study, which was a case of lateral sinus thrombosis with facial palsy. The mortality rate of lateral sinus thrombosis was reported as 10% by Samuel et al. (8). The role of exposing the sigmoid sinus with evacuation of the clot is debatable and currently conservative surgery seems to be sufficient (2). Systemic anticoagulants should be used in selected cases only, such as involvement of the sagittal sinus or a persistent rise in intracranial pressure (15).

There were two cases of extradural abscess and one case of subdural abscess in our study. Neurosurgical procedure was performed initially followed by canal wall down mastoidectomy.

The mortality from otitis media is usually secondary to intracranial complications. Mortality rate has reduced from 75% in the pre-antibiotic period to 5% in the antibiotic period in developed countries (14). The mortality rate in our study was 0.6%. The low mortality rate in our study could be due to the lower incidence of intracranial complications compared to extracranial complications, as well as prompt treatment of patients, improved microsurgical techniques and critical care services in our center.

The limitations of this study are its retrospective nature and the disproportion between the sample sizes of the acute and chronic otitis media groups. In the future, prospective studies on the impact of routinely administrated pneumococcal conjugate vaccine in complications from otitis media may be performed.

Conclusion

The incidence of complications due to chronic otitis media with cholesteatoma is higher as compared to that of acute otitis media and chronic otitis media without cholesteatoma. Extracranial complications are common as compared to intracranial complications. However, multiple complications may occur. Otorhinolaryngologists should be aware about the possibility of masking of the symptoms and the absence of classical clinical presentation with the use of antibiotics.

Ethics Committee Approval: Ethics committee approval was received for this study from the Institutional Review Committee of Institute of Medicine, Tribhuvan University (Approval Date: January 7, 2020; Approval Number: 278(6-11)E2 076/077).

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Protective Effect of Carvacrol against Paclitaxel-Induced Ototoxicity in Rat Model

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Original Investigation

Abstract

Objective: This study aimed to explore whether carvacrol (CV) had a protective effect on paclitaxel-induced ototoxicity from biochemical, functional, and histopathological perspectives.

Methods: Forty Wistar albino male rats were randomly separated into five groups of eight rats. Group 1 was the control group, so Paclitaxel or CV was not administered. Group 2 was administered i.p. CV at 25 mg/kg once a week; Group 3, was administered i.p. paclitaxel at 5 mg/kg once a week; Group 4 was administered i.p. paclitaxel at 5 mg/kg followed (30 min later) by CV at 25 mg/kg once a week; and Group 5 was administered i.p. CV at 25 mg/kg followed (1 day later) by paclitaxel at 5 mg/kg. once a week. The drugs were administered intraperitoneally once a week for four consecutive weeks, and distortion product otoacoustic emissions (DPOAE) tests were performed at the beginning of the study before the first drug administration and at the end of the study after the last drug administration. All rats were sacrificed, and cochleae were removed for biochemical and histopathological analysis.

Results: Biochemical data indicated that paclitaxel caused oxidative stress in the cochlea. Histopathological findings revealed the loss of outer hair cells in the organ of Corti (CO) and moderate degenerative changes in the stria vascularis (SV). It was observed that DPOAE measurements were significantly reduced at high frequencies. In groups which CV was administered together with paclitaxel, these biochemical, histopathological, and functional changes were favorably reversed.

Conclusion: CV may have a protective effect against paclitaxel-induced ototoxicity when given.

Keywords: Carvacrol, ototoxicity, oxidative stress, paclitaxel, animal experimentation

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Introduction

Ototoxicity refers to cellular degeneration and functional impairment of the cochlear and/or vestibular tissues and can lead to transient or permanent hearing loss (1, 2). Presently, drug-induced hearing loss is more frequently reported in clinical findings, especially in patients who have been treated with chemotherapeutic drugs (3). Today, there are no routine procedures or agents recommended for the treatment of chemotherapeutic agent-induced ototoxicity (2).

Paclitaxel, a taxane plant product isolated from *Taxus brevifolia*, is a broad-spectrum antineoplastic agent (4, 5). The damages the agent inflicts on the sensory neurons in the dorsal root ganglia raises questions regarding its effects on peripheral auditory neurons. A few clinical studies were reported on the sensorineural hearing loss effects of paclitaxel (6). Although some researchers have observed the ototoxic effects of some anti-cancer agents such as cisplatin, which is especially well documented, research on the direct ototoxic effects of paclitaxel on the hair cells in the cochlea are limited (2, 4). The reason for the difficulty in understanding the ototoxic effect of paclitaxel may be due to its use in combination with other antineoplastic drugs, such as cisplatin, for which ototoxic effects were documented (7).

Evidence suggests that chemotherapeutic agents cause ototoxicity as a result of the accumulation of

reactive oxygen species (ROSs) such as superoxide and hydroxyl radicals, and the depletion of glutathione (GSH) and antioxidant enzymes (8, 9). Therefore, the use of various antioxidant agents has been the strategy of numerous studies to prevent and restore the ototoxic effects of chemotherapeutic drugs (10, 11).

One of the agents with antioxidant properties is carvacrol (CV), which is a monoterpenic phenol. It is found in the essential oils of many aromatic plants, including, among others, oregano, and thyme. CV is responsible for a wide range of pharmacologic activities, including antimicrobial, antioxidant, and anti-cancer activities (12). Remarkably, CV has high antioxidant activity, and numerous studies have investigated its antioxidant properties (13). Although CV is known to be a primary antioxidant, its role in paclitaxel-induced ototoxicity is unknown, and to the best of our knowledge, no previous studies were reported on this subject.

This study investigated whether CV had protective efficacy against the ototoxicity induced by paclitaxel, from biochemical, functional, and histopathological perspectives.

Methods

Animals

Forty Wistar albino male rats (weighing 250-280 g) were obtained from the Atatürk University Experimental Animal Laboratory of Medicinal and Experimental Application and Research Center. The care and handling of animals were in line with the principles of the Animal Ethical Committee of Atatürk University (Approval Date: August 22, 2016; Approval Number: 42190979-000-E. 1600192974). The rats were kept in standard plastic cages with ad libitum access to standard rat chow and tap water. Until the end of the study, the cages were kept in a room equipped with an air-conditioner set at 22±1˚C and a fully automated lighting system (12 h light/12 h dark).

Chemicals

The CV used in this study was obtained from Sigma-Aldrich (W224511; Sigma-Aldrich Chemical Company; Taufkirchen, Germany). The selected dose of CV was 25 mg/kg (14) and administered intraperitoneally (i.p.) as calculated per weight for each rat.

Main Points

- Ototoxicity is the functional disorder of the cochlear and / or vestibular structures, which is frequently reported in clinical findings, due to the use of chemotherapeutic drugs.
- Carvacrol (CV) is a monoterpene phenol known for its powerful antioxidant properties.
- Based on the data from the rat cochleae, this study showed that CV might have a protective effect on paclitaxel-induced ototoxicity from biochemical, functional, and histopathological perspectives.
- The study suggests that CV may be useful as a preventive option in patients receiving paclitaxel against possible ototoxicity.

Paclitaxel was purchased from Actavis Pharma (Sindaxel; Actavis Drug Co., İstanbul, Turkey) and administered i.p. at 5 mg/kg, as calculated per weight for each rat.

Finally, ketamine hydrochloride was obtained from Pfizer (Ketalar; Pfizer Drug Co., İstanbul, Turkey), and xylazine from Bioveta (Xylazinbio; Bioveta, Ankara, Turkey). An anesthetic mixture was prepared with 10 mg/kg xylazine, and 40 mg/kg ketamine hydrochloride, administered i.p. as calculated per weight to each rat for anesthesia.

Experimental Design

At the beginning of the study, all rats were anesthetized intraperitoneally with an anesthetic mixture (50 mg/kg ketamine hydrochloride-10 mg/kg xylazine) to perform otoscopic examination and measure distortion product otoacoustic emissions (DPOAE). Rats with a pathology detected in the outer ear canal and tympanic membrane, and whose hearing was not normal were excluded from the study. The study consisted of five groups, namely the control group and four experimental groups. Each group contained eight randomly selected rats. The sample size of the study was determined according to similar studies previously conducted (5, 15, 16).

Group 1 - Control group: 1 mL serum physiologic was administered i.p. once a week for four consecutive weeks.

Group 2 - CV group: CV was administered i.p. at 25 mg/kg once a week for four consecutive weeks.

Group 3 - Paclitaxel group: Paclitaxel was administered i.p. at 5 mg/kg once a week for four consecutive weeks.

Group 4 - Paclitaxel + CV group (pre-treatment carvacrol): first a 5-mg/kg dose of paclitaxel was given and 30 min later 25-mg/kg of CV was administered i.p. once a week for four consecutive weeks.

Group 5 - CV + Paclitaxel group (post-treatment carvacrol): first 25 mg/kg CV was given and 1 day later 5 mg/kg paclitaxel was administered i.p. once a week for four consecutive weeks.

The second DPOAE measurements were taken under general anesthesia one day later after the last drug application. The rats were sacrificed to perform the experiments; their temporal bones were dissected, and cochleae were removed. Right cochleae were used for histopathological studies and the left cochleae for biochemical analysis.

Otoacoustic Emissions Measurements

The DPOAE measurements were performed with an Otometrics MADSEN Capella device (Otometrics MADSEN Capella Otoacoustic emissions testing; Natus Medical Denmark ApS) using a suitable probe. The first DPOAE measurements were performed under general anesthesia, after otoscopic examination, and before drug administration in a silent room (in the first week). The second DPOAE measurements were performed af-

ter the last drug application (in the fourth week). Measurements were recorded in the distortion product gram (DPgram) form. In the DPgram measurement, primary stimulus intensities were equalized at 65 dB (L1=L2). The two separate frequencies (f1 and f2) were arranged as f2/f1=1.22 to receive the strongest responses. Furthermore, the DPgram measurements were taken at 996; 1191; 1416; 1679; 2001; 2382; 2832; 3359; 4003; 4755; 5654; 6728; and 7998 Hz. In the DPOAE measurements, values equal to 3 dB and higher for the signal-to-noise ratio (SNR) were evaluated as positive.

Biochemical Investigation of Cochleae

After the left cochleae were removed, cochlear tissues were stored at -80°C until analysis. These tissues were set in liquid nitrogen with a Tissue Lyser II (Qiagen; Hilden, Germany) grinding jars set. All cochlear specimens (about 100 mg of tissue) were homogenized in 1 mL of phosphate-buffered saline (PBS) homogenate buffer. Then, to obtain the supernatant, homogenized tissues were centrifuged, and superoxide dismutase (SOD) activity was measured as described in the literature (17). Values were expressed as units per milligram of protein. GSH levels were determined using the methods described by Sedlak and Lindsay (18) and expressed as nanomoles per milligram of protein. Malondialdehyde (MDA) levels were also measured using a technique described in the literature (19). Concentrations were expressed as nanomoles per milligram of protein, and SOD activity, as well as GSH and MDA levels were measured at room temperature with an enzyme-linked immunosorbent assay (ELISA) reader.

Histopathological Evaluation of Cochleae

After the right cochleae were harvested for histopathological analysis, they were fixed for 24h in 10% buffered formaldehyde. Then, decalcification was done in these tissues with 6% nitric acid. After decalcification was completed, the decalcification solution was washed out under running water for approximately 30 minutes. After routine processes, tissues were embedded in paraffin blocks. These were then sectioned at 5 μm thickness. Sections were transferred onto glass slides and stained with hematoxylin and eosin (H&E). The sections of the cochlear tissues were evaluated under a light microscope by pathologists who were blind to the grouping of samples. Presence of Corti organ (CO) damage was evaluated based on grading system of de Freitas et al. (20), and the grading of CO damage was assessed based on the number of external ciliated cells (ECCs) following de Freitas et al.'s (20) 4-point scoring system:

0: presence of three ECCs with intact nuclei;
1: presence of two ECCs with intact nuclei;
2: presence of one ECC with intact nuclei;
3: loss of CO.

The status of the stria vascularis (SV) was evaluated based on Yazici et al.'s (21) staging system. Staging was assessed based on the degree of cell shrinkage.

According to the staging scoring system, tissues were categorized as follows:

0 = no damage;
1 = slight damage;
2 = moderate damage;
3 = serious damage.

Statistical Analysis

Statistical analysis was performed using the IBM Statistical Package for the Social Sciences v20.0 (IBM SPSS Corp.; Armonk, NY, USA) software. While evaluating the DPOAE results, compatibility with normal distribution was evaluated with the Kolmogorov-Smirnov test. The paired t-test was used to compare the groups before and after the administration in terms of normally distributed data. Data were presented as mean±standard deviation, and $p<0.05$ was considered statistically significant. Histopathological findings were analyzed with the Kruskal-Wallis test and significance was accepted at $p<0.001$. Analyses between two groups were performed with the Mann-Whitney U test with Bonferroni correction. When evaluating the results of the biochemical analysis, comparisons between the groups were made with the one-way ANOVA and Tukey's tests; significance was accepted at $p<0.05$.

Results

Results of DPOAE Measurements

The DPOAE measurements were taken before and after drug administration at 3000, 4000, 6000 and 8000 Hz. Amplitude changes in groups were compared for both the right ear and the left ear (Figure 1). There were no statistically significant differences in pre- and post-treatment DPOAE measurements at any frequency (3000-8000 Hz) in Groups 1, 2, 4 and 5 ($p>0.05$). Also in Group 3, no statistically significant differences were observed in the pre- and post-treatment DPOAE measurements at frequencies of 3000 and 4000 Hz ($p>0.05$), but statistically significant decrease were detected in the post-treatment measurements at 6000- and 8000-Hz frequencies ($p<0.05$).

Results of Biochemical Parameters

The results of the GSH and MDA levels and SOD activity of rat cochleae are shown in Figure 2. In Group 3 MDA levels ($p=0.000$) were significantly increased, while SOD activity ($p=0.000$) and GSH levels ($p=0.000$) were significantly decreased compared to Group 1. Compared to Group 3, statistically significant increases were found in the SOD activity ($p=0.005$, $p=0.007$, $p=0.006$ respectively) of Groups 2, 4, and 5. Compared to Group 3, statistically significant increases were found in the GSH levels (0.002, 0.009, 0.020 respectively) of Groups 2, 4, and 5, whereas statistically significant decreases were found in the MDA levels of Groups of 2 ($p=0.005$), 4 ($p=0.006$), and 5 ($p=0.002$) compared to Group 3. In other words, the level of GSH and the SOD activity in cochlear tissue had significantly decreased in the paclitaxel group, whereas in the CV groups, high GSH levels and SOD activity values were found. Moreover, MDA levels, which are lipid peroxidation indicators, were increased by paclitaxel, while CV prevented this increase with an antioxidative effect and remained close to the control group.

Table 1. Histopathological scoring results of CO and SV damage

	Group 1	Group 2	Group 3	Group 4	Group 5	p
CO damage	0 (0-0)	0 (0-0)	3 (3-3)*	0 (0-0)	0 (0-0)	<0.001
SV damage	0 (0-0)	0 (0-1)	2 (2-2)*	0 (0-0)	1 (1-1)	<0.001

The Kruskal-Wallis test was used for statistical comparisons and p<0.001 was considered significant. The paclitaxel group (Group 3) was compared with the other groups, *p<0.001 marks were used.
CO: corti organ; SV: stria vascularis

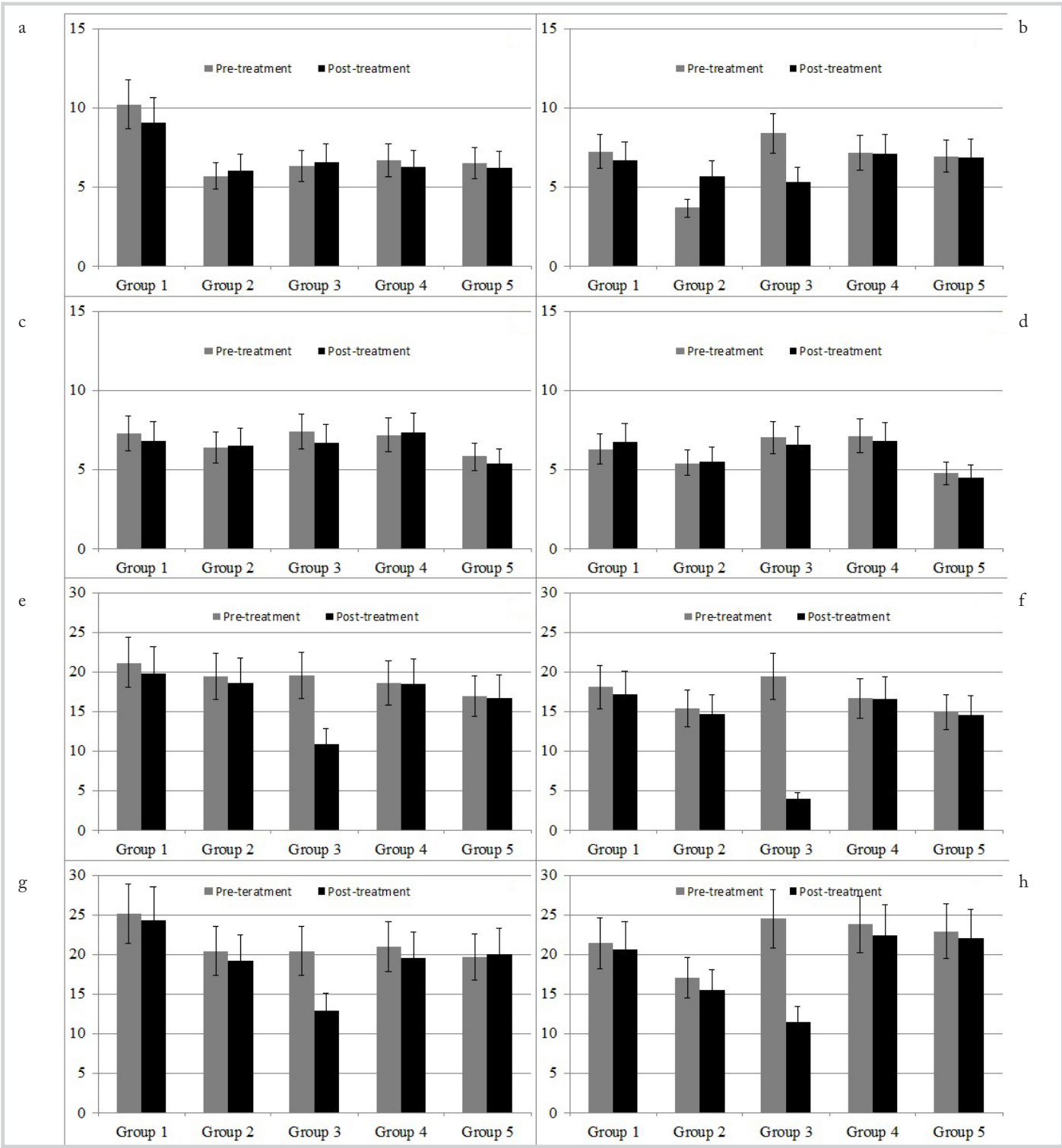

Figure 1. a-h. Average DPOAE amplitudes pre and post drug treatment for each group. (a) at 3000 Hz frequency (right ear); (b) at 3000 Hz frequency (left ear); (c) at 4000 Hz frequency (right ear); (d) at 4000 Hz frequency (left ear); (e) at 6000 Hz frequency (right ear); (f) at 6000 Hz frequency (left ear); (g) at 8000 Hz frequency (right ear); (h) at 8000 Hz frequency (left ear)

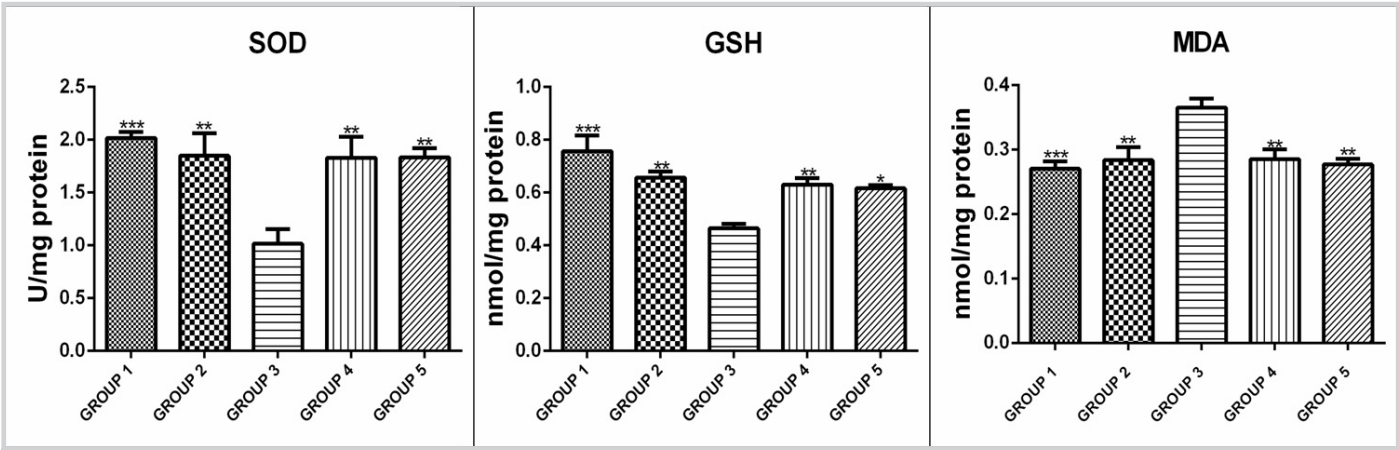

Figure 2. a-c. (a) SOD activity, (b) GSH and (c) MDA levels of the groups subjected to paclitaxel-induced ototoxicity
Statistical comparisons were made using one-way ANOVA followed by Tukey's test. The paclitaxel group was compared with the other groups, *p<0.05, **p<0.01, and ***p<0.001 marks were used. Values are represented as mean±SD

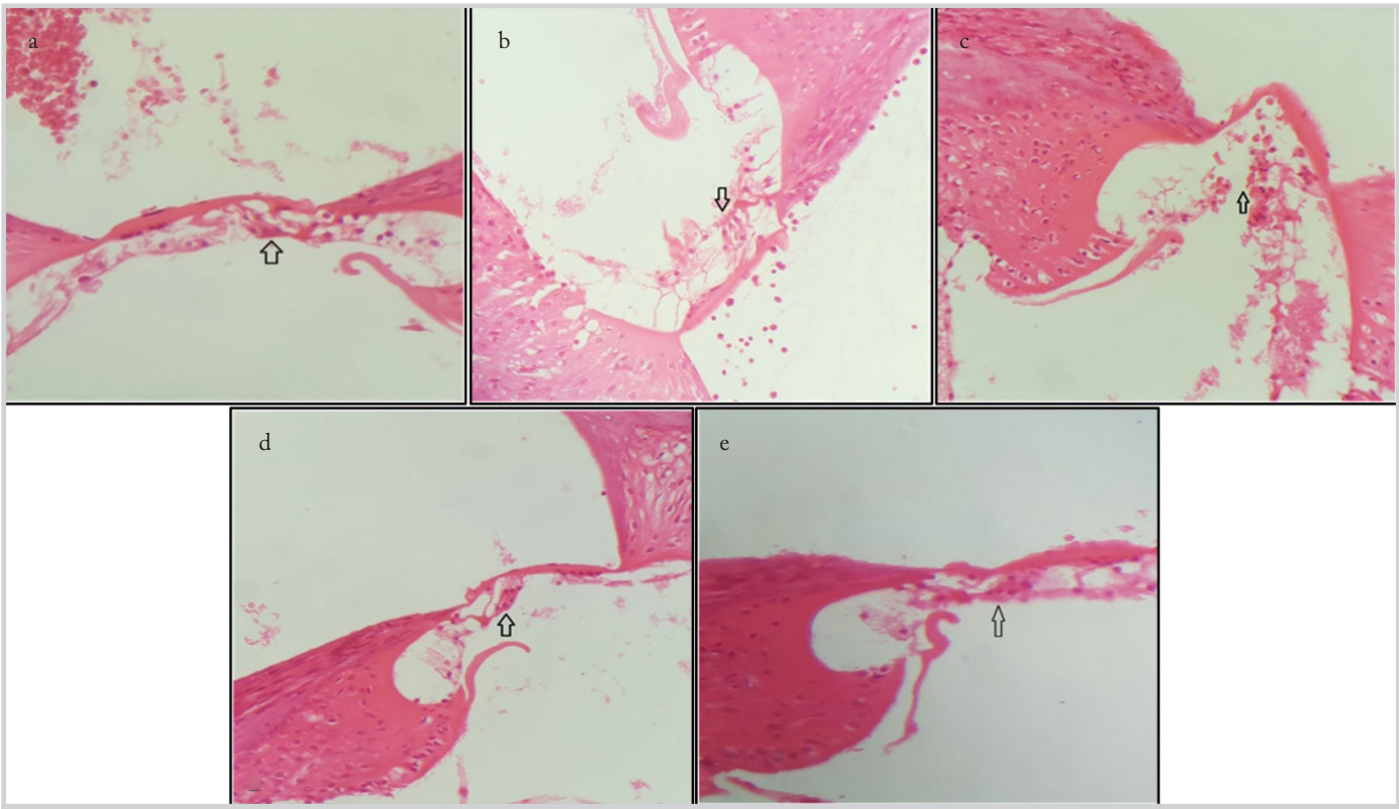

Figure 3. a-e. Stria vascularis sections of all groups. (a) Group 1, (b) Group 2, (c) Group 3, (d) Group 4, (e) Group 5. Dye: H&E Magnification: x400

Results of Histopathological Evaluation

Histopathological scoring results were evaluated for CO according to the grading system described by de Freitas et al. (20) and for SV damage according to the staging system described by Yazici et al. (21). These are presented in Table 1. In the groups 2, 4, 5, CO and SV damage scoring was lower than in Group 3, which was the paclitaxel group (p<0.001). Histopathological examination of sections taken from cochleae were obtained using H&E staining under a light microscope (Figures 3, 4). The histopathological appearance of the cochleae exhibited normal architecture in Groups 1, 2, and 4. Examination of the cochleae in Group 3, however, found significant degeneration characterized by moderate degenerative changes in the SV (Figure 3) and loss of outer hair cells in CO (Figure 4). Finally, in Group 5, outer hair cells were close to a normal histopathologic appearance; however, mild degeneration in SV were observed.

Discussion

This is the first study that investigated the protective effect of CV in a paclitaxel-induced ototoxicity model. The role of CV in ototoxicity was observed by investigating its effect on oxidative stress parameters. The data were also supported with findings from histopathologic changes. Although paclitaxel is a widely used chemotherapeutic agent in the treatment of various cancers

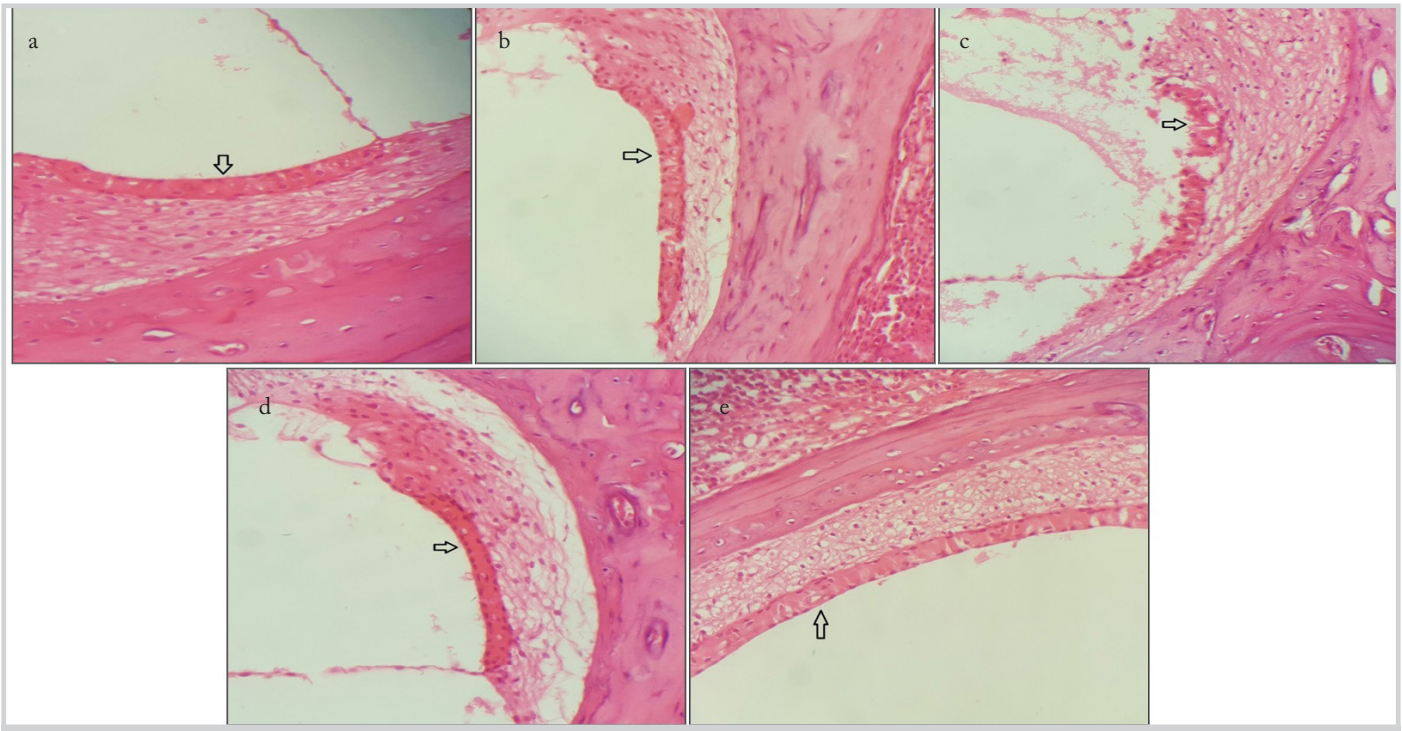

Figure 4. a-e. Corti organ sections of all groups. (a) Group 1, (b) Group 2, (c) Group 3, (d) Group 4, (e) Group 5. Dye: H&E Magnification: x400

(22, 23), there is not much research yet on whether paclitaxel has an ototoxic effect, because paclitaxel is used with other chemotherapeutic agents known to have ototoxic effects (7). This situation conceals the possible ototoxic effects of paclitaxel. Also, whether CV has protective effect on ototoxicity has not been studied to date. Therefore, our study is deemed to contribute to the literature by investigating both the effect of paclitaxel—which is used in the treatment of many cancers—and the effect of CV—which may be a new candidate for the treatment of ototoxicity. The fact that a recent study has already shed light on paclitaxel's ototoxic effects, demonstrates that more studies should be conducted on this subject (5).

Today, there is no routine treatment method and agent used to prevent ototoxicity. The molecular mechanism of chemotherapeutic-drug-related ototoxicity has not been fully elucidated. However, numerous studies exist on the prevention and repair of ototoxicity (2). The basis of these studies is that chemotherapeutic drugs cause ototoxicity due to the uncontrolled increase in ROSs (9). Excessive production of ROSs results in the depletion of GSH and the accumulation of superoxide ions, leading to the inhibition of antioxidant enzymes in the cochlea. Depletion of the antioxidant defense system then causes an increase in lipid peroxidation. The generation of ROSs consequently activates apoptosis and causes cell damage (24). Therefore, antioxidant agents that both prevent the uncontrolled production of ROSs and strengthen the antioxidant defense system are widely used to counteract the ototoxic effect of chemotherapeutics. Several studies report to have used antioxidants such as pomegranate, gallic acid, vitamin E, and curcumin to prevent ototoxicity (5, 10, 11, 21). The presented study aimed to investigate whether CV's known antioxidant properties would have a protective effect on paclitaxel-induced ototoxicity.

CV is a monoterpenic phenol found in the essential oils of many aromatic plants such as, *Thymus vulgaris*, *Origanum vulgare*, *Origanum majorana*, and *Citrus uranium bergama*. It offers a wide range of biological effects that are useful in clinical practice, such as antibacterial, antioxidant, anti-cancer, antifungal, and antiviral properties. It is also worth noting that CV is well known for its strong antioxidant properties compared to other essential volatile oils. The strong radical-scavenging activity of CV was proven in both in vitro and in vivo studies (12). It demonstrated a hepatoprotective effect in a hepatotoxicity study by increasing the activity of enzymatic (superoxide dismutase, catalase, and GSH peroxidase) and non-enzymatic (vitamin C and E) antioxidants (25). Further, CV was observed to prevent lipid peroxidation and increase the endogenous antioxidant defense mechanism in a study on hepatocellular carcinogenesis (26). It was also demonstrated to improve acute pancreatitis with its strong antioxidant effect (13). Whereas the strong antioxidant effects of CV have been shown in some studies, there are no reports in the literature on the use of CV for ototoxicity. To the best of our knowledge, our study is the first to examine the effects of CV on ototoxicity.

In the presented study, an increase in MDA levels, a decrease in GSH levels, and SOD activity were observed in paclitaxel-induced ototoxicity (Group 3). CV exhibited an otoprotective effect by preventing ROS formation and repairing oxidative stress damage (Groups 4 and 5). Histological findings were observed as CO and SV damage in the paclitaxel-treated group (Group 3). In CV-treated groups (Groups 4 and 5), the degeneration caused by paclitaxel improved, and the cochleae had a normal histological appearance.

DPOAE measurements were performed in the first and fourth weeks to support our biochemical and histopathologic findings.

The DPOAE test is a fast, inexpensive, non-invasive, and objective method that is frequently used in experimental studies to determine any damage in the cochlea (27). Based on the DPOAE measurements, significant decrease was observed in the fourth week at 6000 and 8000 Hz in the paclitaxel-administered group (Group 3) compared to the control group (Group 1). However, the decrease observed in the paclitaxel-administered group (Group 3) increased with the effect of CV (Groups 4 and 5) in DPOAE measurements and contributed to results comparable to that of the control group, hence was no significant difference between the before and after measurements. These results suggest that CV has an otoprotective role against paclitaxel-induced ototoxicity. The biochemical, histopathologic, and DPOAE results of the only CV- administered group (Group 2) were not statistically different from the control group. These results indicate the safety of CV in terms of ototoxicity.

This study has clear limitations that warrant consideration. Ototoxicity mainly affects high frequencies, which cannot be completely examined using the DPOAE measurements. Nevertheless, in this study, we observed the DPOAE results up to 8000 Hz. Another limitation is that we could not identify whether the protective effect of CV on a cochlear function to paclitaxel-induced ototoxicity is dose-dependent.

Conclusion

Considering the results which we obtained in rat cochleae, we can say that CV could play a protective role against paclitaxel-induced ototoxicity by lowering elevated ROSs and raising antioxidant enzyme levels. Our results are also supported by DPOAE measurements and histopathological findings, which suggest that CV may be useful as a preventive option in patients receiving paclitaxel against possible ototoxicity. Nevertheless, further studies are needed to determine the most appropriate doses and the indications of CV in clinical use.

Ethics Committee Approval: Ethics committee approval was received for this study from the Animal Ethical Committee of Atatürk University (Approval Date: August 22, 2016; Approval Number: 42190979-000-E. 1600192974).

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Effect of Distal Masseter to Facial Nerve Transfer in Paralytic Patients with Preserved Facial Nerve Continuity on Improving Scaled Measurement of Improvement in Lip Excursion (SMILE): A Vectoral Analysis

Original Investigation

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Abstract

Objective: Distal masseter-to-facial neurorrhaphy is an option to improve smile excursion in facial paralysis patients in the early period without truncating the facial nerve truncus and by ensuring the continuity of the facial nerve. This study aimed to study the effect of distal masseter-to-facial neurorrhaphy on smile excursion.

Methods: Charts of eight patients were retrospectively examined. Screenshots showing the best possible smiles were taken from preoperative videos. Screenshots were taken from postoperative videos showing the best combination of a natural smile on the healthy side and a smile with clenched teeth on the paralytic side. Emotrics and Photoshop software were used for computing vertical, horizontal, and overall excursion from facial landmarks. Scaled measurements of improvement in lip excursion and lip angle was evaluated. Symmetry was evaluated by accepting the healthy side as 100 percent, and the paralytic side was calculated as a percentage of the healthy side.

Results: Five patients had total facial paralysis and three had facial paresis. Mean postoperative follow-up period was 15.0±10.2 months. The average interval between facial denervation and nerve repair was 14.0±4.1 months (range, 11-23). All neurorrhaphies were coapted end-to-end to either the zygomatic or the buccal branch without an interposition graft. Mean postoperative initial movement occurred at 95.5±20.5 days (range, 72-138). Paralytic side to healthy side horizontal excursion changed from preoperative 72.5±17.4% to postoperative 93.4±6.9%. Vertical excursion changed from preoperative 38.4±24.6% to postoperative 89.3±11.8%. Overall excursion changed from preoperative 68.4±19.6% to postoperative 92.9±10.4%. Paralytic side to healthy side mean lip angle changed from 64.7% preoperative to 95.2% postoperatively. All changes were statistically significant ($p<0.05$).

Conclusion: Facial paralysis patients with an asymmetric smile benefit from distal masseter-to-facial nerve transfer and it improves smile excursion dramatically. This effect was especially prominent in the vertical component of the smiling vector.

Keywords: Facial paralysis, facial palsy, facial paresis, masseter nerve, smile excursion, facial reanimation

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Introduction

Facial paralysis is a disabling disease associated with depression and severe decrease in life quality (1). Numerous facial reanimation techniques are described to address facial paralysis. Recently, paralytic patients with anatomically and physically preserved nerve continuity present as a dilemma; two practical approaches are possible: (a) conservatively waiting for spontaneous recovery, (b) or early intervention by connecting additional nerve input from other cranial nerves. Denervation time is a factor that makes the timing of the intervention as crucial as the intervention itself. While recent studies have shown that early intervention resulted in more satisfactory results, current literature tends to stress the importance of early intervention (2). Nerve transfer to the facial nerve trunk offers a trade-off of giving up natural facial nerve healing. Neurorrhaphy to distal branches without truncating avoids this trade-off and makes early nerve transfer a viable option.

The masseter nerve, a motor branch of the trigeminal nerve, is a donor nerve described relatively more

Table 1. Patient data

	Age (years)	Gender	Etiology	Denervation time (months)	Follow up period (months)
Patient 1	23	Female	Salivary gland tumor	12	36
Patient 2	27	Female	After acoustic neuroma surgery	11	23
Patient 3	17	Female	After brain tumor surgery	15	16
Patient 4	66	Female	Ramsay Hunt Syndrome	23	13
Patient 5	30	Male	Facial schwannoma	16	12
Patient 6	47	Male	After acoustic neuroma surgery	11	8
Patient 7	9	Male	Idiopathic recurrent facial nerve paralysis	12	6
Patient 8	30	Male	Idiopathic recurrent facial nerve paralysis	12	6

recently by Spira (3) in 1978. It was first described as a donor nerve for free gracilis muscle transfer, but its utilization solely in nerve grafting was reported numerously in the literature (4, 5). Its proximity to the surgical field eliminates the need for an interposition graft, and thereby prevents extra morbidity, allowing for theoretically faster and better healing due to single-anastomosis.

This study aimed to evaluate the effects of distal masseter-to-facial nerve transfer in facial palsy patients with preserved facial nerve continuity on improving smile excursion.

Methods

This study was approved by Başkent University Institutional Review Board (Approval Date: June 16, 2020; Approval Number: KA20/241) and supported by Başkent University Research Fund. Informed consent was obtained from all patients. Records of patients who were operated on from January 2018 to January 2020 were examined consecutively. All patients were operated on by the first author. Truncation of the facial nerve truncus was a criterion for exclusion from the study. Patients were consecutively included, and patient records and surgical notes were retrospectively reviewed. Denervation time and follow-up period were noted for each patient.

Operative Technique

The operative technique was based on the cadaveric studies by Collar et al. (6) and Borschel et al. (7). In all cases, the masseteric nerve was identified through a limited, minimally invasive dissection following a limited preauricular incision rather than a parotidectomy-like approach. Landmarks of the subzygomatic triangle were marked 3 to 1 cm measurement as explained by Borschel et al. (7).

Main Points

- Distal masseter-to-facial nerve transfer is a viable option for early reinnervation without truncating the main facial nerve truncus.
- Mean postoperative initial movement occurred at the third postoperative month.
- Facial paralysis patients with asymmetric smile benefit from distal masseter-to-facial nerve transfer, which improves smile excursion; this improvement is especially dramatic in the vertical vector.

A preauricular incision was carried out with a 15-blade, and subcutaneous dissection was carried out bluntly. Buccal and zygomatic branches that approximate the origin of zygomatic muscle on the zygomatic bone were identified with blunt dissection of a delicate hemostat parallel to the distal branches of the facial nerve. After the recipient branch was identified, the masseter nerve was explored. Basic nerve stimulator (Stimuplex® HNS12 Nerve Stimulator, Braun Medical Inc.; Melsungen, Germany) was used to identify the nerve branches. The masseter nerve in the masseter muscle was dissected; abundant masseter nerve dissection was ensured for a tension-free coaptation without the need for an interposition graft. Approximately 4 to 5 nylon sutures (10-0) were used for end-to-end coaptation. All cases were finalized with fibrin sealant (Baxter International Inc.; Illinois, USA). Minivac drains were removed and all patients were discharged on the first postoperative day.

Evaluation

Evaluations were based on the screenshots taken from the standardized preoperative and postoperative videos of patients. Screenshots of the best possible smiles were taken from the preoperative videos. Screenshots of the best possible combined smiles with a natural smile on the healthy side and a smile with clenched teeth on the paralytic side were taken from the postoperative videos. The Emotrics sofware (Emotrics Software, Mass Eye and Ear; Boston, MA, USA) was used to automatically mark the facial landmarks such as the iris and the facial midline with the software's artificial intelligence algorithm (8) (Figure 1). Best possible smile photos were marked, and scaled measurements of improvement in lip angle and lip excursion (SMILEs) were calculated by vectorial analysis as previously described (9).

Statistical Analysis

On the healthy side, vertical excursion was marked (y), horizontal excursion was marked (x), and overall excursion was marked (z). On the paralytic side, vertical excursion was marked (y'), horizontal excursion was marked (x'), and overall excursion was marked (z'). Vectors on the healthy side were accepted as 100%, and the paralytic side was scale measured relatively as (x/x') x100. Preoperative and postoperative values, and change rates were compared with the Wilcoxon Signed Ranks test. IBM Statistical Package for the Social Sciences version 24 (IBM SPSS Corp.; Armonk, NY, USA) was used for statistical analysis. P values lower than 0.05 were accepted as statistically significant.

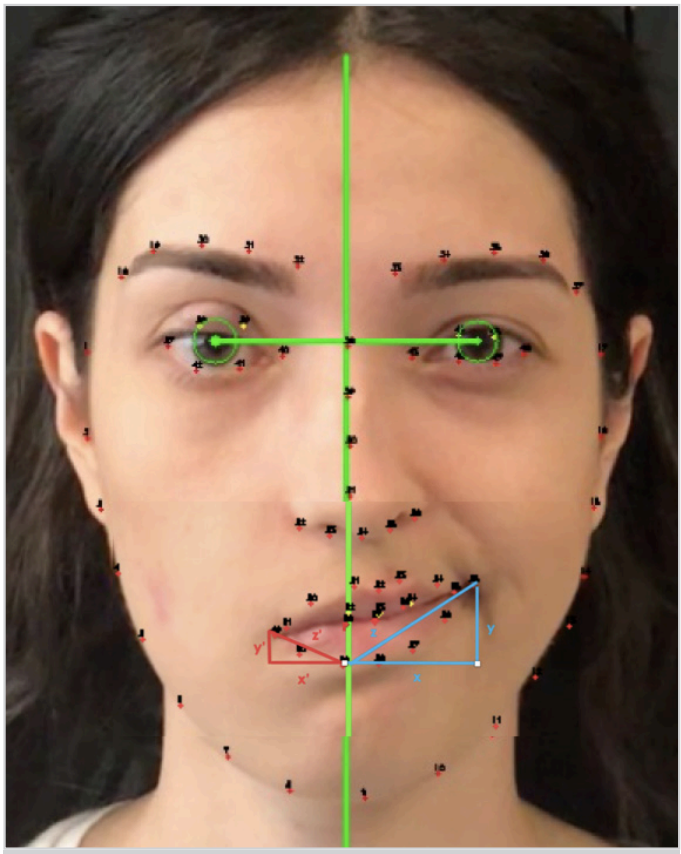

Figure 1. Marking of facial landmarks in Emotrics software and vectoral analysis in pixels via Photoshop

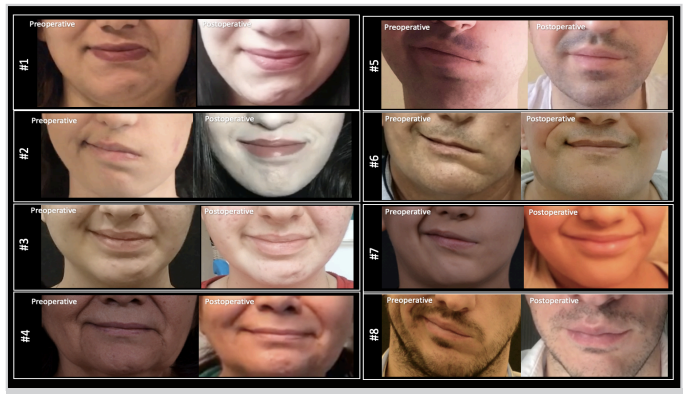

Figure 2. Preoperative and postoperative images of best possible smile

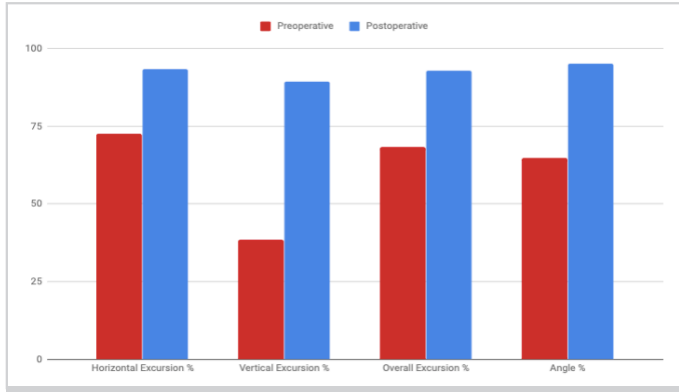

Figure 3. Evaluation of smile excursion vectors and lip angles

Table 2. SMILE vectoral analysis before and after distal masseterofacial anastomosis

	Preoperative (%)	Postoperative (%)	p	z
Horizontal lip excursion	72.5	93.4	0.036	-2.100
Vertical lip excursion	38.4	89.3	0.012	-2.521
Overall lip excursion	68.4	92.9	0.036	-2.100
Lip angle	64.7	95.2	0.012	-2.521

Table 3. Pros and cons of using the masseter nerve

Pros	Cons
Proximity to surgical field	Masseter muscle atrophy associated
asymmetry	
Eliminating the need for an interposition graft	Tonus
Fast healing	Need for adaptation and physical therapy
Strong excursion	
Minimal morbidity	

Results

Five patients had total facial paralysis, and three had facial paresis; etiologies are detailed in Table 1. Four patients were male and four were female (Table 1). Mean time between facial denervation and nerve repair was 14.0±4.1 months (range, 11-23). Mean postoperative follow-up period was 15.0±10.2 months. All neurorrhaphies were coapted end-to-end to either the zygomatic or the buccal branch without an interposition graft. Two of the eight patients received additional static suspension with tensor fascia lata graft for a better resting facial symmetry. Three of the eight patients had undergone upper eyelid gold weight placement at another center, and two had adjunctive upper eyelid golden weight placement. Two patients (25%) complained about temporary painful and limited oral opening in the early postoperative period, and these were resolved without intervention. Slight atrophy of the masseter was present in some patients, but none opted for filler or fat augmentation.

The mean time to postoperative initial movement was 95.5±20.5 days (range, 72-138) (Figure 2). Paralytic side to healthy side horizontal excursion percentage changed from preoperative 72.5±17.4% to postoperative 93.4±6.9%. Vertical excursion percentage changed from preoperative 38.4±24.6% to postoperative 89.3±11.8%. Overall excursion percentage changed from preoperative 68.4±19.6% to postoperative 92.9±10.4% (Figure 3). Paralytic side to healthy side mean lip angle changed from 64.7% preoperative to 95.2% postoperatively. All changes were statistically significant ($p<0.05$); results are further detailed in Table 2.

Discussion

End-to-end hypoglossal (XII) nerve transfers have historically been the workhorse technique in for facial animation. Jump and other modified hypoglossal nerve transfer procedures were

introduced to eliminate (a) the need for an interposition graft, (b) a possible hemiglossal atrophy, and (c) the synkinetic mass movement of the face (10).

These three complications and extra donor morbidity can be avoided with masseterofacial anastomosis. Comparison of masseterofacial and hypoglossofacial nerve anastomosis revealed superiority for masseterofacial nerve anastomosis in dynamic movements, whereas, at rest, the hypoglossofacial anastomosis was found slightly better (11). Our study results show that masseterofacial anastomosis of distal facial branches provided a powerful and symmetric smile (Table 2). Nevertheless, it should be noted that adjunct procedures may be required in complete flaccid paralytic patients with a chubby face to achieve symmetric resting tonus. A combination of tensor fascia lata static sling is a viable option.

Our study included the patients with intact facial nerve and branches and those with truncated facial nerve were excluded. This is to say that our results represent a very homogeneous population, and this makes our results reliable. We compared pre- and postoperative maximum smile images of each patient. To better understand the differences between patients with intact facial nerve and truncated facial nerve, further investigations with a larger sample size are needed.

Masseteric nerve input ensures fast healing due to proximity, which is essential for patients with long denervation time. Nerve transfer to distal facial branches also ensures the continuation of spontaneous healing of the anatomically preserved nerve continuity. Unlike crossfacial nerve grafting, which ensures synchronous facial movements, using the new masseterofacial anastomosis for harmonious mimicry requires learning, practice, and cortical adaptation (Table 3). Rehabilitation and functional recovery after masseterofacial nerve anastomosis is a process that can be expedited with physical therapy (12).

Nevertheless, there are reports in the literature that show that masseter muscle co-activation occurs naturally when smiling. This was shown with electromyography measurements (13). Compared to those performed with non-facial nerve donors, masseterofacial nerve anastomosis seems to be an advantageous option in terms of spontaneity and synchronicity.

There are many surgical treatment strategies for paretic patients about which they were informed during their preoperative visits. The decision-making process was carried out together with the patient. From the patient's aspect, masseterofacial anastomosis alone has the advantages of being a single-stage surgery and not involving the healthy side of the face.

Hontanilla and Marre (14) reported about their experience with masseterofacial anastomosis in nine incomplete paralysis patients that were comparable to our patient series. Frey et al. (15) reported the "facial upgrading" in paretic patients with a procedure which they called distal end-to-side cross-facial nerve grafting (CFNG). In this procedure, distal facial nerve branch of the donor side is transected and coapted end-to-end to the sural nerve graft. Distally, the sural nerve graft is coapted end-to-side following an epineural window. With this procedure, native facial nerve axonal input is neither lost nor at risk on the paretic side (15).

Biglioli et al. (16) reported 20 midface paresis cases treated with dual innervation in two stages. The first stage is CFNG to the preauricular region. The second stage is end-to-end masseterofacial anastomosis accompanied by end-to-side coaptation of CFNG distal to the coaptation site of masseterofacial anastomosis.

Besides the debates on the surgical management of facial paralysis cases, follow-up and objective recovery measurements are not well described. Outcome measures in facial palsy are mainly evaluated by patient-reported outcome measures, clinician-graded scoring systems, and objective software analysis. Patient-reported measures are subjective, but an excellent way to understand the social burden of the effects of facial paralysis. Clinician-graded scoring systems are almost subjective, but none of the scaling systems satisfies all (17).

House-Brackmann (HB) staging is a quick clinical grading system and has been used widely worldwide for many years. However, the HB grading system is mainly dependent on the evaluator and remains insufficient, such as the mouth assessment subpart is far from being adequate in evaluating changes in smile excursion. Thus, the use of a computer-based objective evaluation system has been described in the literature (8, 15, 18).

Many evaluation systems were introduced in the late 1990s, and there has been a focus on the use of objective metrics in dynamic facial reanimation (19-23). In 2000s, computer analysis software have been used to analyze facial movements (20-22). Developments in artificial intelligence and high-resolution photography/video technology made it possible to evaluate the effects of any facial intervention with more precision.

In 2012 Hadlock and Urban (23) reported using software to detect total facial weakness and zonal facial weakness. They found the software very useful in distinguishing healthy subjects from facial paralysis patients and concluded that the software could be used in rehabilitation follow-ups. Hontanilla et al. (18) reported FACIAL CLIMA evaluation, mainly an optic camera system that recognizes facial movements such as smiling, mouth puckering, and eye closing.

This optical system automatically defines and calculates the vectoral changes with three cameras. However, we have used the Emotrics software that allows user verification for the reference points and calculates the vectors on a static image. That Emotrics software was developed using the standard face databases allow the results to be more realistic, whereas FACIAL CLIMA calculates the dynamic vectoral changes in the same patient. The disadvantage of Emotrics is the need for high-quality photographs (18).

Since objective was to address and repair the symmetry, the SMILE system which evaluates the smile relative to the healthy side was used. One of the limitations of this study is the limited sample size, but on the other hand, it brings novelty in terms of reporting quantitative outcomes of an intervention using novel outcome measures. Using quantitative outcome measures and artificial intelligence software is crucial for the comparison of different interventions. These tools have the potential to offer a universal and automated outcome measures in the future.

Conclusion

Facial paralysis patients with asymmetric smile benefit from distal masseter-to-facial nerve transfer, which improves smile excursion dramatically. Further studies are required to confirm these findings.

Ethics Committee Approval: Ethics committee approval was received for this study from the Başkent University Institutional Review Board (Approval Date: June 16, 2020; Approval Number: KA20/241).

Informed Consent: Informed consent was obtained from the patients who participated in this study.

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Photodynamic Therapy as a New Treatment for Chronic Rhinosinusitis - A Systematic Review

Review

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Abstract

This review examines the latest evidence for photodynamic therapy (PDT) in treating chronic rhinosinusitis. MedLine, EMBASE and TRIP Database searches were conducted using the terms: "photodynamic" or "phototherapy" or "photo" and "sinusitis" or "rhinosinusitis," date range January 2000 to May 2020. A total of 192 records were initially identified, after duplicates and exclusions, 9 full papers and 3 abstracts were included. All study types including in-vitro, animal and human studies were evaluated. Whilst there is in-vitro evidence for the efficacy of PDT's bactericidal effect on drug resistant bacteria and biofilm viability, there are few clinical studies. PDT is a promising area of research, but larger, focused studies looking at the safety, delivery, efficacy, and patient selection are required before it can be considered a viable treatment for CRS.

Keywords: Phototherapy, photodynamic therapy, paranasal sinus diseases, sinusitis, alternative therapies

Introduction

Chronic rhinosinusitis has a significant impact on patient quality of life and productivity, affecting 5-12% of the general population (1). It is classified as chronic when the core symptoms persist beyond 12 weeks; is difficult to treat or is recalcitrant when symptoms persist despite appropriate medical and surgical treatment. Recent work has focused on defining CRS as either primary or secondary based on the type of the inflammatory disease or endotype. The overall aim is to allow for tailored treatment regimens focusing either on a primarily infective or an inflammatory (type 2) cause. The previous classification of CRS with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP) is no longer favored, as polyps can present in both types of CRS. The classification for primary and secondary CRS is summarized in Figure 1 which has been adapted from Grayson et al. (2). The pathophysiology of CRS is complex; we must consider the various possible predisposing and causative factors.

Allergy and Asthma

Allergy and asthma in the context of CRS have been extensively studied. The presence of inhalant allergy has been found to be significantly higher in both CRS patients with and without polyps (3). The prevalence of allergy appears to vary with phenotype; central compartment atopic disease and allergic fungal rhinosinusitis have stronger associations than CRS with and without polyp groups. There is a strong association between asthma and CRS, especially in those with both CRS and allergic rhinitis (4). A United Kingdom study showed the prevalence of asthma to be 44.9% in CRSwNP, 21.2% in CRSsNP, compared to the 9.95% in controls (3).

Environmental Irritants

It is hypothesized that the pollutants can affect ciliary function including mucociliary clearance (5), predisposing to repeated infection and inflammation. It has been demonstrated that air pollutants are correlated with CRS symptom severity, with CRSsNP being the most affected cohort (6). Studies have shown that occupational exposure to dust from metals, textiles and paper are associated with CRS (6-8).

Fungi

Like bacteria, fungi can form biofilms and secrete toxins, but their role in CRS pathogenesis is yet to be fully elucidated. The role of fungi, like Aspergillus, in subtypes where fungal balls occur and in allergic fungal rhinosinusitis is clearer (9). Ex-vivo studies have shown that *Aspergillus niger* stimulation resulted in increased pro-inflammatory cytokines like IL-6 (10). Shin et al. (11) demonstrated that CRS patients showed exaggerated humoral

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and cellular responses to common airborne fungi, particularly Alternaria, and that this could explain the chronicity of inflammation seen in CRS.

Virus

It is hypothesized that viral infection could initiate or exacerbate CRS; coronavirus was the most commonly found virus in patients with CRS (12). In a study from Iran with 76 CRS patients undergoing endoscopic sinus surgery, 33% were found to have at least one of rhinovirus and respiratory syncytial virus (13). Ex-vivo studies have demonstrated that rhinovirus infection can be associated with exacerbation of CRS, including increased susceptibility to secondary microbial infection and impairment of mucociliary clearance (14, 15).

Bacteria and Biofilms

Part of the pathophysiology of CRS is thought to be secondary to bacteria like *Staphylococcus aureus*, where colonization results in the disruption of the normal mucosal barrier and the promotion of immune dysregulation, further amplified by antibiotic drug resistance and biofilm formation (16, 17). In addition, the overgrowth of "bad" bacteria displaces those bacteria that are considered part of a healthy microbiome, resulting in microbial dysbiosis (16).

Patients with CRS have been found to lack normal sinus mucociliary defense mechanisms and to be colonized by multi-drug resistant bacteria that form biofilms within sinus cavities and continue to cause chronic inflammation (18-20). Methicillin-resistant *S. aureus* (MRSA) and multidrug resistant *Pseudomonas aeruginosa* are found in the clinical isolates of CRS patients and are a cause of antibiotic treatment failures (18, 20). Traditional treatment with steroids, oral antibiotics, nasal douches, and sinus surgery are less effective in this population. For these patients and those with other types of CRS, alternative therapies must be evaluated, as supported by the recommendations from EPOS 2020 (21).

A relatively new area of interest involves the use of light therapies. Light therapies include laser, near infra-red illumination, ultraviolet (UV) light therapy and photodynamic therapy (PDT). To date, PDT has been most effective in the treatment of cancer. It is often used to treat actinic keratosis and basal cell carcinoma. It has also been shown to be effective in early stage squamous cell carcinoma of the oropharynx, nasopharynx and larynx, although a clinical role for PDT in this context is yet to be defined (22). In animal studies, PDT has proven effective in treating chronic wound infections by suppressing bacterial growth (23).

Main Points

- Photodynamic therapy involves applying a photoactive agent to a surface and then irradiating this area with light. It has been shown to have anti-inflammatory, anti-bacterial and anti-neoplastic effects.
- Photodynamic therapy aims to reduce the bacterial load causing chronic infection and immune dysregulation in chronic rhinosinusitis
- Photodynamic therapy has been shown to be highly effective *in-vitro* and *in-vivo* against bacteria implicated in chronic rhinosinusitis
- The clinical studies to date have shown promising results through improvements in both objective and subjective outcome measures, with no unacceptable adverse effects
- Randomised control trials are required to fully assess the short and long term efficacy of this treatment modality

PDT uses a photosensitizing agent solution to prime the surface area covered by biofilm, then light at a specific wavelength is administered to activate this solution. This triggers the formation of reactive oxygen species (ROS) which have anti-bacterial, anti-inflammatory and anti-neoplastic downstream activity (24). The ROS damage cell walls, allow translocation of further activated solution and damage inner organelles, resulting in apoptosis (25). This cell death mechanism is an entirely different pathway to that of antimicrobials and might offer an alternative option for combatting multi-drug resistant organisms (26, 27). Commonly used photosensitizers include ultra-methylene blue (selectively binds to microbial cell walls and biofilms) and aminolevulinic acid variants. In addition, in-vitro studies have shown that unlike antibiotics, bacteria do not develop resistance to repeated photodynamic therapy treatments (28). There is also much evidence that PDT can disrupt biofilm by further reducing bacteria viability and increase sensitivity to antibiotics (29).

There are numerous studies to support the bactericidal effect of photodynamic therapy on drug resistant and biofilm forming bacteria (30-37). Whilst this technique may have a role in treating CRS, the research in this area is only just evolving and there is a need to evaluate its potential in treating CRS. This review will focus on the studies that are relevant to PDT and the treatment of CRS.

At present, approved devices include the Sinuwave photodisinfection system licensed in Canada, and a study using this device in human studies has been conducted by Desrosiers et al. (38). Rhinolight is a device that emits UV and visible light and is predominantly being used in the treatment of allergic rhinitis in centers across Hungary and Germany (without the application of a photoactive agent). Its evidence base centers on allergic rhinitis and the ex-vivo study discussed here uses this device in conjunction with a photoactive agent (39, 40). The other studies that have been evaluated in this review use light emitting devices in lab-based settings, not commercially produced or licensed for use in humans.

This review article examines the current evidence base for use of photodynamic therapy in the treatment of chronic rhinosinusitis.

Materials and Methods

MedLine, EMBASE and TRIP database searches were conducted in May 2020 using the following terms: "photodynamic" or "phototherapy" or "photo" and "sinusitis" or "rhinosinusitis", date range January 2000 to May 2020.

Inclusion criteria:
- Original scientific contributions
- Studies that employ photodynamic therapy (agent that acts as a photosensitizer and irradiation with light which could be in the form of a laser, LED, etc.)
- Use bacterial isolates from the human sinus or CRS patients for in-vitro studies
- Must investigate the use of PDT in the context of CRS or bacteria that cause CRS

Exclusion criteria:
- Studies that use light therapy alone without a photosensitizer
- Studies that use planktonic or other research strains of bacteria (they may be referenced to provide supporting evidence but are not included in the main table of papers)
- Insufficient information/conference abstracts (Three conference abstracts, all by Desrosiers et al. (38, 41, 42), have been included as they provide preliminary information on the results in human studies)
- Reviews, books etc. that refer to other studies
- Studies that are not directly looking at CRS, but investigate other conditions like allergic rhinitis or acute rhinosinusitis

AK and RS independently assessed the title and abstracts of the identified articles to determine relevance. Any disagreement was resolved by discussion with senior authors. Database searching identified 192 records that met the search terms (Figure 2). After duplicates were removed, 161 abstracts were screened, of which 106 were then excluded. Fifty-five full text articles were assessed for eligibility against the inclusion and exclusion criteria. After 43 articles were excluded, nine full papers and three abstracts were selected to be included in the review. Some of the full text articles that were excluded (n=43) have been referred to in the paper where they support the evidence of the included articles, for example mechanisms of delivery of PDT.

Regarding in-vitro studies, the papers included here are all relevant to investigating the effect of photodynamic therapy on biofilm forming bacteria, although not all use strains of bacteria from CRS patients or from the sinus cavity. The studies that use other isolates have not been included in the main table of results. According to the American Society of Microbiology (2010), a new approach has to prove an efficacy of 3 $\log_{10}$ reduction of colony forming units (CFU) before being able to use the term "antibacterial" (43).

Results

The studies included six in-vitro, one ex-vivo, one animal case report, three human case series and one randomized control trial (RCT), these are summarized in Table 1.

Pre-Clinical Studies (Laboratory)

In-vitro Studies

Preliminary studies by Zhao et al. (44) demonstrated antimicrobial properties of 5-aminolevulinic acid (ALA) mediated PDT on biofilm forming strains of *S.aureus* and *S.epidermidis*. The application of PDT appreciably reduced bacterial growth of *S.aureus* and *S.epidermidis* isolated from CRS patients. This was measured as a significant reduction in bacterial growth (measured as log reduction in colony forming units) when compared with control groups of the same planktonic strains of bacteria. In the biofilm *S.aureus* experiment, the mean log colony forming units (lgCFU) was 8.68±0.05 (control group), 6.90±0.96 (experiment group) ($t=3.68$, $p<0.05$); and in biofilm *S.epidermidis* experiment the data was 8.67±0.05 (control group), 7.29±0.61 (experiment group, $t=5.07$, $p<0.01$). They present clear methodology for how biofilm was cultured and how conditions were controlled, including how the optimal photosensitizer concentration and light intensity were found. The CRS patients included here had received medical therapy prior to endoscopic sinus surgery (ESS), secretions from the middle meatus were sampled in order to obtain *S.aureus* and *S.epidermidis* strains for this in-vitro experiment. No further details regarding the type and length of medical treatment received by this cohort of CRS patients were included in the manuscript.

This study is supported by research undertaken by Biel et al. (45) using drug resistant strains of *P. aeruginosa* and MRSA. They demonstrated that PDT reduced the CRS polymicrobial biofilm by >99.9% after a single treatment. For the 300μg/mL concentration of the photoactive agent methylene blue (MB) there was a 6.5 log reduction of antibiotic-resistant multi-species bacterial biofilms after a single PDT treatment. When they used a higher MB concentration and lower light parameters, they achieved greater than seven logs of bacteria kill using two PDT light treatments. They showed clear methodology for each of the experimental groups and used an objective automated tool for counting colonies; however, the authors do not offer limitations or a critical appraisal of the study.

More recently, this group created an anatomically correct maxillary sinus model in order to conduct the same experiment using MB and 670 nm non-thermal activating light (46). Again, they showed a 99.9% reduction in biofilm for both *P. aeruginosa* and MRSA strains after one treatment as measured by log reduction in CFU. The model was created from human CT scans, and dimensions were taken as the average of 10 random male and female maxillary sinuses. The mixed species biofilm inoculum was pipetted into sterile silicone models and then allowed to shake for 24 hours. It is not clear how these results using silicone models and artificially grown biofilm can be extrapolated to how biofilm forms on human ciliated respiratory mucosa of the maxillary sinus, and the authors have recognized this as a limitation. The have shown methodological rigor by using 11 different treatment combinations to assess the effects of different concentrations of ethylenediaminetetraacetic acid (EDTA), EtOH and methylene blue. They were able to show that low concentration of EDTA added to MB results in improved PDT efficacy of killing biofilm forming bacteria.

A further study by Zhang et al. (47) in 2017 investigated the effect of ALA mediated PDT on *S.aureus* biofilm, and the effect

Table 1. Summary of Studies of Photodynamic Therapy and Chronic Rhinosinusitis

Title	Author Date Country	Cohort	Level of evidence/ Study type	Outcomes	Key Results	Study Limitations/Risk of Bias
In-vitro study of photodynamic therapy of antibiotic-resistant staphylococcus from patients with chronic rhinosinusitis	Zhao et al. (44) 2016 China	45 patients treated medically for CRS requiring FESS, mucus taken from middle meatus. 13 S.aureus and 16 *S.epidermidis* strains were identified. 5-aminolevulinic acid mediated PDT was applied to these strains as well as Planktonic strains.	Level 5 In-vitro	Mean IgCFU for experiment and control groups of planktonic and patient *S.aureus* and *S. epidermidis* strains.	In the biofilm *S.aureus* experiment, the mean lgCFU was 8.68±0.05 (control group), 6.90±0.96 (experiment group) (t=3.68, P<0.05); and in biofilm *S.epidermidis* experiment the data was 8.67±0.05 (control group), 7.29±0.61 (experiment group, t=5.07, P<0.01).	In-vitro study, only 2 major biofilm forming strains of bacteria used. Single outcome measure (IgCFU), clinical applicability requires evaluation.
Antimicrobial photodynamic therapy treatment of chronic recurrent sinusitis biofilms	Biel et al. (45) 2011 USA	Antibiotic resistant planktonic bacteria and fungi, and polymicrobial biofilms of *Pseudomonas aeruginosa* and MRSA were grown on silastic sheets and treated with a methylene blue photosensitizer and 670nm non-thermal activating light. Cultures of the planktonic microorganisms and biofilms were obtained before and after light treatment to determine efficacy of planktonic bacteria and biofilm reduction.	Level 5 In-vitro	Kill rate as measured by log CFU reduction in bacteria.	The CRS planktonic microorganism and biofilm study demonstrated that aPDT reduced the CRS polymicrobial biofilm by >99.9% after a single treatment. For the 300 μg/mL MB concentration there was 6.5 log reduction of antibiotic-resistant multi-species bacterial biofilms after a single PDT treatment. Using a higher MB concentration (500 μg/mL) and lower light parameters achieved greater than 7 logs of bacteria kill using two PDT light treatments.	Multi-organism biofilm was treated with PDT rather than single organism biofilm.
5-aminolevulinic acid-mediated photodynamic therapy and its strain-dependent combined effect with antibiotics on Staphylococcus aureus biofilm	Zhang et al. (47) 2017 China	Study investigating the effect of 5-aminolevulinic acid with light emitting diode 633nm (ALA mediated PDT) on S.aureus. Biofilm forming MRSA and MSSA strains were isolated from CRS patients undergoing endoscopic sinus surgery. MRSA and MSSA were treated with ALA-PDT, compared with ALA-PDT combined with antibiotics (vancomycin, netilmicin or cefaclor). Control groups included no treatment, ALA alone, and light irradiation alone.	Level 5 In-vitro	Kill rate as measured by log CFU reduction in bacteria.	ALA-PDT was found to significantly inactivate *S.aureus* biofilm across all 15 strains, mean 5.75log10CFU/ml reduction in viable count; the effects were similar in the MSSA and MRSA groups. When ALA-PDT was combined with antibiotics (vancomycin, netilmicin or cefaclor) the bactericidal effect increased for at least 9 out of the 15 strains. They hypothesize that PDT breaks the sessile structure of biofilm leading to recovery of antibiotic sensitivity, although it is not clear why this happens in a strain dependent way.	The addition of antibiotics seems to have an additive effect to the PDT. Experimental groups were small, the conclusion that the effect in MRSA and MSSA strains is not significantly different may not be repeatable. The authors cannot explain why the additive effect of antibiotics is seen in some strains and not in others.

Table 1. Summary of Studies of Photodynamic Therapy and Chronic Rhinosinusitis (Continue)

Title	Author Date Country	Cohort	Level of evidence/ Study type	Outcomes	Key Results	Study Limitations/Risk of Bias
Development and characterization of erythrosine nanoparticles with potential for treating sinusitis using photodynamic therapy	Garapati et al. (48) 2015 USA	Study of erythrosine mediated PDT in *S. aureus* cells using nanoparticle delivery system. In one arm of the experiment, cells were incubated with free erythrosine drug, and the other arm with erythrosine nanoparticles. The control arm was *S. aureus* only plus irradiation. Cells in all arms were irradiated at 6 time points with an LED (530nm).	Level 5 In-vitro	Kill rate as measured by log CFU reduction in bacteria.	The uptake of erythrosine in *S.aureus* cells from nanoparticles and pure drug was approximately 14.83±0.15 and 0.60±0.19 g per mg of protein, respectively. This indicates the ability of bacteria cells to internalize erythrosine nanoparticles is better than the free drug. Photodynamic inactivation of erythrosine nanoparticles after 8, 16 and 24 h, was significantly higher compared to pure erythrosine. This could be attributed to the sustained released of erythrosine from nanoparticles.	This nanoparticle mediated method of PDT could potentially mean that reactive agent is only inserted into a sinus cavity once, and then the irradiation can be repeated at several time points to achieve maximum bactericidal effect. Further in-vivo studies are required to test the efficacy and safety of this method.
The effect of antimicrobial photodynamic therapy on human ciliated respiratory mucosa	Biel et al. (52) 2012 USA	Study of aPDT treatment of EpiAirway™ (in-vitro airway tissue model that originates from normal, human-derived tracheal/ bronchial epithelial cells) was performed. Treatment groups included a non-treatment control, laser light alone, photosensitizer alone, and therapeutic photosensitizer and light combination (aPDT).	Level 5 In-vitro	Histomorphological evaluation of the EpiAirway specimens.	The EpiAirway™ histologic study demonstrated no histologic alteration of the respiratory cilia or mucosal epithelium in any of the treatment groups.	Unclear how accurately in-vitro airway tissue model reflects normal sinus ciliated respiratory epithelium.
Photodynamic therapy of antibiotic-resistant biofilms in a maxillary sinus model	Biel et al. (46) 2013 USA	Antibiotic resistant polymicrobial biofilms of P. aeruginosa and MRSA were grown in an anatomically correct novel maxillary sinus model and treated with a methylene blue/EDTA photosensitizer and 670nm non-thermal activating light. Cultures of the biofilms were obtained before and after light treatment to determine efficacy of biofilm reduction.	Level 5 In-vitro	Kill rate was calculated as surviving CFU/ ml in experimental conditions versus control (no light and no photosensitizer) and expressed as a log10 reduction from control for each individual organism.	PDT reduced the CRS polymicrobial biofilm by >99.99% after a single treatment. The best treatment results in biofilm reduction were achieved with PDT using the photosensitizer 1.25mM EDTA + 5% EtOH + 0.03%MB in the presence of 670nm light resulting in a 5 log10 (99.99%) reduction in *P. aeruginosa* biofilm and a 3.1 log10 (99.9%) reduction in MRSA biofilm after a single treatment. Low concentrations of EDTA added to MB results in improved PDT efficacy of multispecies biofilm bacterial kill.	In-vitro study using anatomically correct model based on CT scans. As the model is not lined by respiratory epithelium it is unclear as to what degree this reflects human physiology.

Table 1. Summary of Studies of Photodynamic Therapy and Chronic Rhinosinusitis (Continue)

Title	Author Date Country	Cohort	Level of evidence/ Study type	Outcomes	Key Results	Study Limitations/Risk of Bias
Ultraviolet light and photodynamic therapy induce apoptosis in nasal polyps	Nemeth et al. (40) 2012 Hungary	Ex-vivo study nasal polyp (NP) tissue was surgically collected from 21 consecutive patients with CRS associated with NP. The removed polyps were cut into pieces and tissue samples were irradiated in-vitro by different doses of combined ultraviolet and visible light (UV/VIS: 280-650nm) and by selective ultraviolet and visible light (sUV/VIS: 295-650nm). PDT was performed by pre-sensitizing tissue samples with 5-delta-aminolevulinic acid (DALA) then irradiated with visible light (VIS: 395-650nm). Tunel assay was applied to detect apoptosis of epithelial and inflammatory cells in irradiated and control nasal polyp tissue samples.	Level 5 Ex-vivo	Apoptosis rate of cells.	UV/VIS light significantly increased epithelial cell and subepithelial leukocyte apoptosis compared to control groups. PDT treatment showed the highest surface epithelial cell apoptosis rate as well as subepithelial leukocyte apoptosis rate compared to all other groups.	This study applies treatment to tissue in a non-physiologic environment and provides results only relating to the CRSwNP cohort.
Temporary regression of locally invasive polypoid rhinosinusitis in a dog after photodynamic therapy	Osaki et al. (51) 2012 Japan	Antivascular photodynamic therapy (PDT) using benzoporphyrin derivative monoacid ring A was applied in one dog with CRS and polyps, 8 months after initial presentation and after failed steroid treatment.	Level 5 Animal case report	CT findings, symptom recurrence.	Short term improvements in symptoms and scan findings up to 11 months post treatment.	In this single case report the subject needed multiple PDT therapies. The improvements appeared to be short lived. Frontal trepanations were used- a method not used by the other studies. Not evident how applicable the results are to human CRS treatment.

Table 1. Summary of Studies of Photodynamic Therapy and Chronic Rhinosinusitis (Continue)

Title	Author Date Country	Cohort	Level of evidence/ Study type	Outcomes	Key Results	Study Limitations/Risk of Bias
Phototherapy for chronic rhinosinusitis	Krespi et al. (53) 2011 USA	A prospective randomized study with 23 symptomatic post-surgical CRS patients with positive cultures was conducted. Two groups (GR1 and GR2) were treated with NILI. GR1 was treated with a 940nm laser, while GR2 was treated with a topical photoactive agent, indocyanine-green, followed with 810nm laser. Saccharin test was performed 1 week following treatment.	Level 4 Case series	Nasal endoscopic scoring (NES), SNOT-20 scores and cultures-positivity / log reduction.	Significant improvement in SNOT scores in both groups. Of the 8 cultures in group 2, post treatment 2 were clear of bacteria and 2 showed significant log reduction. In group 2 there was a 50% reduction in mean NES score. Saccharin transit test for group 2 post treatment was normal in all cases. Two of the 23 patients experienced pain during treatment which subsided after reverting from continuous to pulsed mode.	Small group of test patients. Patients had varying degrees of pre-treatment surgery. NES scoring and saccharin tests were only performed in group 2. Saccharin transit test results suggest no adverse effect on ciliary movement. Little information provided regarding patient characteristics of the two groups, randomization, blinding and follow-up protocol. It appears the experiment was run in the first group which influenced how the second group experiments were conducted.
Sinuwave photo-disinfection for the treatment of refractory chronic rhinosinusitis: a case series	Desrosiers et al. (38) 2013 Canada	Twenty-nine sinuses (13 frontal, 6 ethmoid, 10 maxillary) in nine patients with recalcitrant CRS persisting following technically successful FESS have been treated with the Sinuwave™ photo-disinfection system.	Level 4 Case series		Short term follow-up has shown no delayed complications and somewhat surprisingly, resolution of disease in several patients.	Conference abstract- full results not published yet.
Evaluation of the safety of antimicrobial photodynamic therapy (aPDT) for refractory chronic rhinosinusitis	Desrosiers et al. (42) 2016 Canada	Of the 44 trial patients, 31 were randomized to receive aPDT and a total of 43 treatments were delivered to 154 sinuses (52 frontal, 48 maxillary, 54 ethmoid).	Level 4 Case series-safety study	Pre and post treatment endoscopic visualization, CT imaging, ophthalmologic evaluation, olfactory testing.	aPDT of the paranasal sinuses can be safely performed in post endoscopic sinus surgery sinus cavities. No instances of ocular dysfunction or visual loss occurred. There was no trauma at the level of the surrounding sinus mucosa, and in several patients, there was resolution of disease.	Conference abstract- full results not published yet.

Table 1. Summary of Studies of Photodynamic Therapy and Chronic Rhinosinusitis (Continue)

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Antimicrobial photodynamic therapy for chronic rhinosinusitis	Desrosiers et al. (41) 2016 Canada	Prospective, randomized controlled trial of 47 patients at 2 clinical centers with a 2:1 randomization model. Twenty-three patients with chronic rhinosinusitis without nasal polyps (CRSsNP) and 24 with chronic rhinosinusitis with nasal polyposis (CRSwNP) unresponsive to medical and surgical therapy were randomized to treatment: a single treatment with aPDT or 2 treatments with aPDT separated by a 4-week interval, or control: endoscopic irrigation with saline.	Level 1 RCT	SNOT-22, endoscopic mucosal score, UPSIT smell test, conventional bacteriology, and Lund-Mackay endoscopic scores.	aPDT treatment improved symptoms and disease specific quality of life, with the greatest effect occurring in the CRSwNP group receiving 2 treatments (endoscopic sinus score improvement 47% at 6 months, p=0.007). aPDT treatments were well tolerated, with the most frequent adverse event being a temporary mild pressure in the treated sinus.	Conference abstract- full results not published yet. The only RCT evaluating both CRSwNP and CRSsNP cohorts. Study uses a variety of objective and subjective outcomes. The follow up time is only 6 months and has a moderate sample size.

IgCFU: log number of colony forming units; CRS: chronic rhinosinusitis; RCT: randomized controlled trial; FESS: functional endoscopic sinus surgery; PDT: photodynamic therapy; EDTA: ethylenediaminetetraacetic acid; CT: computerized tomography; NILI: near infrared laser illumination.

when combined with antibiotics. Ten methicillin sensitive *S.aureus* (MSSA) and 5 MRSA biofilm forming strains were isolated from CRS (with and without polyps) patients undergoing endoscopic surgery. The authors do not detail the clinical history or the previous treatments of these patients who were sampled.

ALA-PDT was found to significantly inactivate *S.aureus* biofilm across all 15 strains, mean 5.75$\log_{10}$CFU/mL reduction in viable count; the effects were similar in the MSSA and MRSA groups. Through the live/dead staining they were able to show that in the ALA-PDT group, the dead cells were predominantly distributed in the upper layer of the biofilm, this could be due to lower concentration of photosensitizer in the inner lay or inability of light to penetrate these regions. When ALA-PDT was combined with antibiotics (vancomycin, netilmicin or cefaclor) the bactericidal effect increased for at least 9 out of the 15 strains. They hypothesize that PDT can break the sessile structure of biofilm resulting in increased antibiotic sensitivity, the authors cannot explain why the added effect with antibiotics is seen in some strains and not others. Regarding the similar effect of ALA-PDT in MSSA and MRS biofilms, the authors recognize that small experimental groups were used and therefore these results may not be generalizable, and further studies are required.

Garapati et al. (48) investigated the role of erythrosine nanoparticles in PDT. They offer detailed and thorough methodology regarding the development of their erythrosine-loaded PLGA (biodegradable polymer) nanoparticle delivery system. They demonstrated that by using nanoparticles to deliver erythrosine inside MRSA cells (from human sinus), there was significantly better uptake of erythrosine than using the free drug (14.83 micrograms per mg of protein compared with 0.6). After 1 hour of incubation, the uptake of erythrosine was ~25 times higher in the presence of erythrosine nanoparticles compared to the free drug. MRSA cells with free erythrosine drug (group 1) and those with erythrosine nanoparticles (group 2) were irradiated at 6 time points with an LED (530 nm). The control groups were MRSA alone, and MRSA plus LED irradiation. There was no effect on MRSA viability in the control groups. At 0.5- and 2-hour time points, groups 1 and 2 produced similar rates of MRSA inactivation. At 8, 16 and 24 hours, photodynamic inactivation of MRSA was significantly higher for group 2. At 16 hours in group 1 there was 5-fold reduction in mean log10CFU/mL compared with complete loss of viability in group 2. They found erythrosine nanoparticles (and irradiation) were highly effective in killing MRSA cells and this could be attributed to the sustained release of erythrosine from nanoparticles. The paper deduces that the nanoparticle system of delivering photoactive reagent into the cells will have more effective bactericidal activity compared with neat reagent. They propose that erythrosine nanoparticles could be delivered into a sinus cavity by using a powder insufflation technique, and that potentially a patient could undergo repeat light therapy without the need for further delivery of the erythrosine, as it is being released continuously from the nanoparticles. They acknowledge that whilst they have shown success in the in-vitro setting, in-vivo studies are required to evaluate the safety and efficacy of the erythrosine nanoparticle delivery system.

Other *In-vitro* Studies (Supporting Evidence)

A more recent study by Parasuraman et al. (49), supports the hypothesis that PDT is more effective when the photosensitizer is delivered into bacterial cells using nanoparticles. They used toluidine

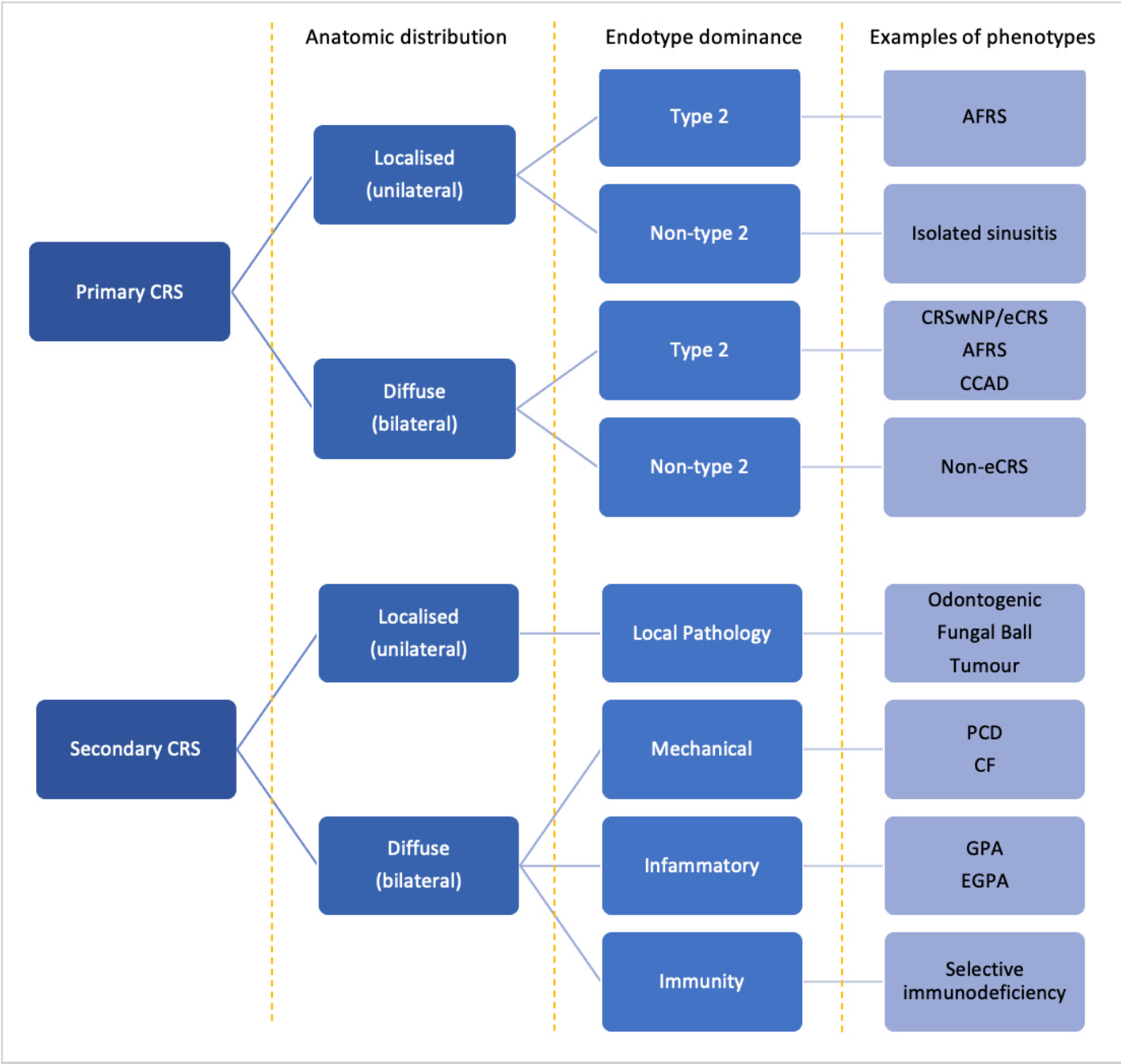

Figure 1. Classification of Primary and Secondary Chronic Rhinosinusitis (adapted from Grayson et al. [2])

blue (TB) encapsulated in mesoporous silica nanoparticles and a red diode laser (670 nm), on *P.aeruginosa* and *S.aureus* (not isolated from the sinus). The study demonstrated significant benefit of using TB in nanoparticles compared with TB alone in terms of reactive oxygen species production, cell inactivation, cell viability and importantly biofilm formation. This is a comprehensive and well-designed study that looked at many outcomes to determine efficacy; these included detection of reactive oxygen species, cell viability, extracellular polymeric substances quantification, protein leakage, lipid peroxidation, biofilm inhibition and anti-biofilm efficiency (live and dead cells) using confocal laser scanning microscopy.

Gandara et al. (50) investigated the effect of toluidine blue (TB) and photodynamic inactivation using 635 nm laser, and the additive effects of using near-infrared treatment (980 nm laser) and proteinase K treatment. Applying TB as the photosensitizer to *S.aureus* biofilm (research strain), and then applying consecutive treatment with 980nm and 635nm lasers produced the largest reduction in biofilm viability (4.5-log viable count decrease), which was significantly more than the effect of TB alone or TB with only one of the lasers. This group proposed that enzymatic digestion of biofilm components using proteinase K could enhance the effect of PDT. When biofilm was treated with proteinase K before TB-PDT there was increased reduction in bacteria CFU counts compared with TB-PDT alone (4.3 vs. 5.46 logs CFU/mL, respectively). This study highlights the additive effect of multiple laser treatment and enzyme treatment in further reducing biofilm viability in an in-vitro setting. The authors

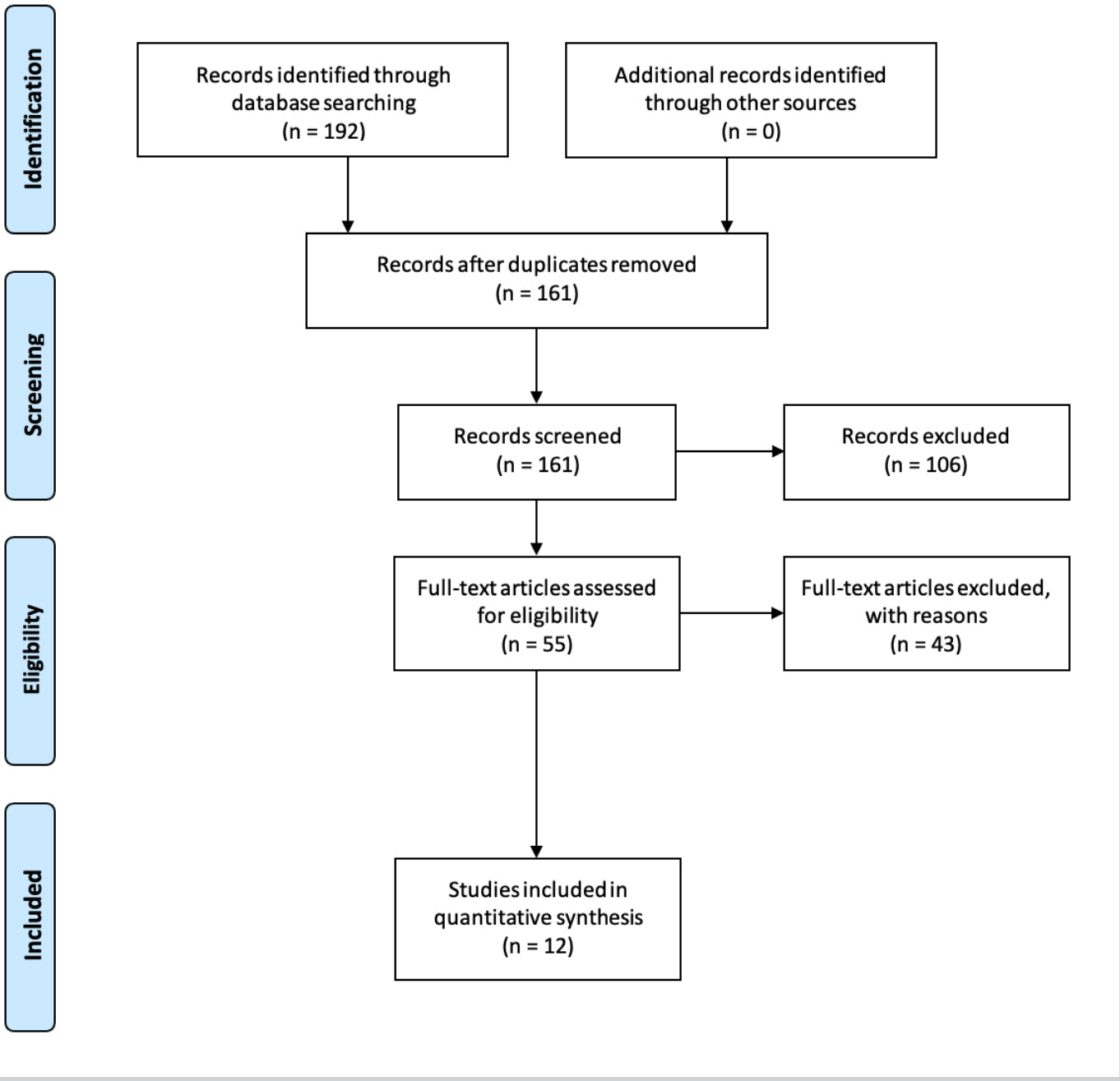

Figure 2. PRISMA Flow Diagram for Systematic Review

recognize that the therapeutic window for near infrared diode lasers is narrow to avoid thermal damage to the host tissue, and this must be further investigated with regards application on human respiratory mucosa that is both safe and with high bactericidal efficacy. They highlight that in-vitro studies investigating the effects of PDT use wide ranging concentrations of photosensitizer and selected wavelengths of light and there it is difficult to compare efficiencies between various studies to obtain mechanistic conclusions.

***Ex-vivo* Study**

Nemeth et al. (40) in 2012 performed an ex-vivo study on polyps taken from 21 consecutive CRS patients undergoing ESS. Patients were excluded if they used certain medication in the four weeks prior, including corticosteroids and leukotrienes. However, no details regarding the clinical history or prior medical or surgical treatment are described. Combinations of ultraviolet and visible light or photodynamic therapy using 5-delat-aminolevulenic acid were applied to the tissue samples using the Rhinolight device. The phototherapy group showed the highest rate of apoptosis of surface epithelial cells (80%) and subepithelial inflammatory cells (70%).

A major limitation of this study is that it is ex-vivo, where harvested polyps are experimented on, it is therefore not clear whether these results reflect in any way what occurs in-vivo in CRS patients with polyps and what the safety profile of the photosensitizing agent or the light irradiation would be. The au-

thors show that for control samples there were smaller numbers of apoptotic surface epithelial cells and subepithelial leukocytes and describe that the numbers seen in the treatment groups were significantly higher than that of the control groups. The authors do not comment on the fact that the polyp tissue being ex-vivo could certainly affect cell viability and susceptibility to light and PDT treatments, potentially skewing the results reported here compared with what would happen in-vivo.

Animal Case Report

A Japanese group have trialed the use of PDT in a dog with CRS and nasal polyps. Osaki et al. (51) describe the case of a dog with disease affecting the nasal cavity and frontal sinuses, which had failed steroid therapy. In this case, antivascular photodynamic therapy (PDT) using benzoporphyrin derivative monoacid ring A (BPD-MA) was administered intranasally via intravenous catheters fitted with cylindrical diffusers, and fibers with microlens inserted through small trephinations of the skin. After 15 minutes of instilling the photosensitizing agent, 690 nm laser light emitted by diode laser was applied via the fibers. After the first treatment there was resolution of symptoms and improvement of computerized tomography (CT) scan findings, however three months later symptoms recurred, and the dog was given a further course of treatment. The subject received four treatments over the space of 11 months. Whilst this case report showed improvement in clinical signs and symptoms after each PDT treatment using BPD-MA, these were clearly short lived. In terms of side-effects, post procedural facial swelling was reported after each treatment, lasting a few days each time and did not require any treatment. This study describes a new technique whereby PDT can be used to treat frontal sinus disease through percutaneous trephinations; although clinically it will be more pragmatic to deliver PDT endonasally via a frontal sinusotomy procedure. This mechanism for treatment would require careful evaluation in human subjects and it is yet unclear if any of the results or analysis would be applicable to the management of CRS in humans.

Safety Studies

The safety of photodynamic therapy has been evaluated by Biel et al. (52) on an in-vitro tissue airway model. They tested PDT using methylene blue and Sinuwave technology on EpiAirway™; this histologic study demonstrated no histologic alteration of the respiratory cilia or mucosal epithelium in any of the treatment groups. It is not evident how representative EpiAirway is of in-vivo respiratory epithelium, so it remains unclear how much these results can be extrapolated.

Desrosiers et al. (41) evaluated the safety of using PDT in human subjects. A conference abstract only gives a summary of the results (full study has not been published). Forty-three PDT treatments were delivered to 154 sinuses. Outcomes included pre and post treatment endoscopic visualization, CT imaging, ophthalmologic evaluation, and olfactory testing using the University of Pennsylvania Smell Identification Test (UPSIT). There were no episodes of ocular dysfunction or mucosal damage. The most frequently reported side effect was transient mild pressure over the treated sinus.

Clinical Studies

In a study by Krespi et al. (53), 23 patients were randomized to receiving laser (940 nm) alone (group 1) or laser (810 nm) and topical photosensitizing agent indocyanine-green (group 2). Post treatment saccharin transit tests for both groups were normal, suggesting no adverse effect on ciliary movement. In the PDT group, Sino-Nasal Outcome Test-20 (SNOT-20) scores dropped by 41% (p=0.0003) and nasal endoscopic scores (NES, based on severity of inflammation, ostial patency and crusting) halved (p=0.0005). In group 1, two of 13 patients were culture negative post treatment, and in group 2, two of 10 patients were culture negative. For the patients where cultures remained positive, there was no detail regarding the log reduction in bacterial growth, and the authors recognized that not measuring bacterial growth qualitatively was a limitation.

There were no serious adverse effects, some experienced minor discomfort during laser illumination, and two patients felt pain associated with heat that subsided when changing from a continuous to a pulsed method of light therapy.

The RoB2 Cochrane tool was used to assess risk of bias in this clinical study. A major limitation was they did not include a control arm. Patients with persistent CRS symptoms, with and without polyps, with at least one prior ESS surgery were recruited; the overall sample size was small. The paper does not offer further details regarding the clinical or surgical history of these patients, and therefore it is unclear whether the two groups were similarly matched in this regard. Patients were assigned to each group by consecutive recruitment randomly to one arm until the group was complete (n=13), then to the other arm. The severity of patient symptoms and endoscopic findings, along with response to treatment guided the number of treatments administered for each patient; it is not clear whether this followed a protocol or was at the discretion of the clinician. The mean follow-up time was 2.8 months, with a range of 2-6 months; it is not evident whether there was a standard follow up protocol; certainly, variable time after treatment could affect the reported outcomes and potentially the magnitude of change in either the SNOT-20 or NES scores.

It appears that experiments were performed consecutively for the two groups, rather than in parallel, so the results of the first study (group 1) appear to have influenced conducting the second study (group 2) experiments. Nasal endoscopic scoring was carried out in group 2 to "record the encouraging endoscopic results demonstrated in group 1." In addition, saccharin transit tests were only carried out in group 2. It is not clear whether the nasal endoscopic scoring was carried out by the same clinician each time, or whether scores were independently checked, and could be considered subjective depending on the clinician's experience; and if different clinicians carried out NES then inter-observer variability needs to be accounted for.

The study appears to have a design where experiments have been carried out consecutively and the first group 1 experiments have influenced how experiments and tests were carried out in the second group. The experiments should have been carried out in parallel using the same protocol. It is also unclear whether patients, clinicians or those carrying out the study were blinded to the type of treatment received.

Whilst there is a lot of missing information regarding the randomization process, the approach in blinding, how the similarity of the characteristics in the two groups were ensured, and how missing data was dealt with, we can conclude that there are considerable concerns regarding risk of bias, and this should be taken into account when interpreting the results and conclusions.

Canada has approved the use of Sinuwave technology for delivering photodynamic therapy in chronic rhinosinusitis. Desrosiers et al. (38) have pioneered the research in this field and after a small case series in 2013, this group conducted the first randomized control trial in 2016 (42). The results have only been published in conference abstract form and the full study results are yet to be published. Each treatment consisted of application of the photosensitizing agent to a previously operated sinus cavity and then illumination with a custom fiber-optic light diffusing balloon catheter. They recruited 23 CRS patients without polyps and 24 CRS patients with polyps to this study. Patients were randomized to PDT or to endoscopic irrigation with saline. Pre and post treatment measures included Sino-Nasal Outcome Test-22, endoscopic mucosal score, UPSIT smell test, conventional bacteriology, and Lund-Mackay endoscopic scores. The study showed PDT treatment improved symptoms and disease specific quality of life, the greatest improvement was in the CRS with polyps group receiving two treatments (endoscopic sinus score improvement of 47% at 6 months, p=0.007).

Discussion/Clinical and Research Consequences

Photodynamic therapy is a new technology that has been used in anti-cancer treatment and might have a role in the treatment of CRS. Studies suggest efficacy in both in-vitro and in-vivo settings, with safety studies so far demonstrating no unacceptable adverse effects.

Clinical studies have shown an improvement in objective and subjective outcome measures in patients with CRS. These studies have only used small sample sizes with follow up times of maximum six months and therefore do not demonstrate the potential long-term benefits or side-effects of PDT.

The studies discussed here use a variety of photosensitizing agents and light emitting devices (Sinuwave and Rhinolight) at different wavelengths. Further studies evaluating combinations of photosensitizing agents at different concentrations, along with each light emitting device at different wavelengths needs to be trialed in human subjects to understand the optimum setting for the eradication of antibiotic resistant biofilm forming bacteria. In addition, most of the clinical studies to date have compared groups of patients receiving different light therapies with no control arm. Studies with control arms receiving no therapy or other traditional medical therapy should be conducted.

The future of PDT will rely on further studies which accurately evaluate the long-term efficacy and sustainability of this intervention using both objective and subjective measures. The ideal study would be a large RCT with appropriately selected CRS patients (with primary and secondary CRS) followed up for more than one year. Evaluation methods should include quantitative measures of bacterial growth, CT scan findings, nasal endoscopic scoring, ciliary activity, olfactory assessment, and subjective measures including the SNOT-22 questionnaire.

Limitations

This review is limited by the lack of existing research, and the quality of included studies, especially clinical trials. Whilst photodynamic therapy is already being used successfully in other domains of medicine and there is in-vitro evidence for the efficacy of PDT, there is little evidence yet to fully support PDT as a viable treatment in CRS patients.

The in-vitro and ex-vivo studies evaluated here have used relatively small experimental groups and different photosensitizers and wavelengths of light. Therefore, it is difficult to compare the in-vitro studies to one another. It is yet unclear how the results of in-vitro studies that have used laboratory-grown biofilm from CRS isolates and/or silicone maxillary models can be extrapolated to the treatment of CRS in humans. Therefore in-vivo studies based on the in-vitro methods used are required to fully assess efficacy, durability, and safety. The clinical studies that have been conducted so far either have insufficient information regarding methodology or considerable risk of bias.

Conclusion

Research in CRS to date have shown that the factors in CRS pathophysiology include the sino-nasal microbiome, host immunity and mucosal barrier. Photodynamic therapy aims to reduce the bacterial load causing chronic infection and immune dysregulation. Preliminary data suggests that PDT is likely to be safe and has proven effective in-vitro. Further clinical research is required to evaluate the safety and efficacy of photodynamic therapy compared with traditional treatment, and how a healthier nasal microbiome can be restored.

The ultimate goal for research into PDT should be to demonstrate an ability to significantly improve the burden of CRS disease and identify the patients or the endotypes of the disease that are most likely to respond. For the treatment to reach clinical practice it will need to be proven as safe, effective, practical, and reproducible. Whilst this may take several years there is enough pre-clinical and early data for cautious optimism in this novel treatment modality.

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Respiratory Protective Equipment for Healthcare Providers During Coronavirus Pandemic: "Nec Temere, Nec Timide"

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Review

Abstract

In otorhinolaryngology-head and neck surgery, there are several routine and surgical procedures applied to the upper airway that generate droplets and/or aerosols. Therefore, otorhinolaryngology-head and neck surgeons are at higher risk of being exposed to viral content. The COVID-19 pandemic has shaken the world with approximately 30 million affected cases and more than 900.000 deaths officially reported in more than 200 countries/regions from March 11th, 2020 to date (September 12th, 2020). All healthcare providers working at the frontlines of the fight against the COVID-19 are at risk of contracting the virus. In this review, we discuss the efficacy of the different types of respiratory protective equipment and remind about the surgery-based respiratory protection strategies in otorhinolaryngology and head and neck surgeries in the light of the latest literature.

Keywords: Otorhinolaryngology, COVID-19, contagious infection, healthcare provider, personal protective equipment, virus disease

Introduction

An infectious respiratory disease caused by severe acute respiratory coronavirus-2 syndrome (SARS-CoV2) which emerged at the end of 2019 has resulted in a worldwide health crisis known as the Coronavirus-2019 disease (COVID-19). On March 11th, 2020, the World Health Organization (WHO) issued a global pandemic warning for COVID-19 (1). Coronavirus-2019 is a highly contagious virus with an *R0* value of 1.4-5.5 (2). It is known that the transmission routes of SARS CoV-2 are direct (person-to-person), indirect (formite), and droplet (>5 mm) contacts. Currently, it is known that the highest viral load of SARS-CoV-2 is in sputum and upper airway secretions (3). The virus is predominantly spread by droplets. Droplet transmission is via respiratory particles that are larger than 5 µm in diameter and have a tendency to travel less than 1 m. Therefore, a limit of 2 m for contact is mandatory. Some authors also advocated that SARS CoV-2 is transmitted by viable viruses in aerosol particles (<5 mm) that suspend in the air (airborne transmission) (4-6).

To date (September 12th, 2020), approximately 30 million patients with COVID-19 were officially reported in more than 200 countries/regions with more than 900.000 deaths. All health-care providers (HCPs) who are working at the frontlines of the fight against COVID-19 are at risk of being infected the virus. Unfortunately, more than 3,000 HCPs in China, 9,282 HCPs in the U.S., and 20% of HCPs in Italy have been infected (7, 8). As seen in the SARS outbreak in 2003, personal protective equipment (PPE) is known to be effective in reducing nosocomial infection risks (9). Although PPE usage can vary according to national resources, the Center for Disease Control and Prevention (CDC) and the WHO recommended that HCPs should wear PPEs against droplet-based transmission. Unfortunately, different research showed that HCPs are at high risk of self-contamination while removing or disposing of the PPE (10, 11). Moreover, several medical procedures may generate aerosols that might travel over distances beyond 2 m, even though the airborne behavior of COVID-19 is uncertain (12).

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In otorhinolaryngology-head and neck surgery, there are several routine and surgical procedures applied to the upper airway that generate droplets and/or aerosols. Therefore, otorhinolaryngology-head and neck surgeons are at higher risk of being exposed to viral content. Respiratory protection should be ensured to correspond to the potential level of airborne transmission to reduce the risk of contagion during aerosol-generating procedures (13, 14).

Currently, different types of masks (surgical and filtering facepiece [FFP] masks) and equipment (elastomeric respirators, powered air-purifying respirator [PAPR]) are used for respiratory protection. Unfortunately, our knowledge about these masks and equipment is limited, and this may lead to confusion about using the appropriate option. Therefore, we aimed to review the efficacy of different types of masks and respiratory protective equipment and remind about the surgery-based respiratory protection strategies in otorhinolaryngology and head and neck surgeries.

Surgical Mask

A surgical mask is not a respiratory protective equipment, even though it is an effective equipment for the protection of patients against droplets of HCPs and vice versa. It adapts loosely to the face and forms a barrier against droplets. However, it is not designed to protect the wearer against airborne infectious agents. It is known from yearslong experiences that the test pathogen for the effectiveness of a surgical mask is the *Staphylococcus aureus*. When the sizes of SARS-CoV-2 and *Staphylococcus aureus* are compared, SARS-CoV-2 is 10-50 times smaller. Therefore, it is structurally not an ideal barrier for COVID-19 contagion. However, it is noteworthy that the size may not be as critical as it is assumed, because the viruses are transported by droplets (15).

Respiratory Protective Equipment

Respiratory protective equipment is any mask or device that is designed for the protection of the wearer from different airborne hazards and infectious agents. Respiratory protective equipment is divided into two groups: air-supplying and air-purifying respirators (Figure 1).

Main Points

- Otorhinolaryngology-head and neck surgeons are at higher risk of being exposed to viral content. Respiratory protection should be ensured to correspond to the potential level of airborne transmission to reduce the risk of contagion during an aerosol-generating procedure.
- A surgical mask is effective against the droplet transmission of infectious agents; however, it does not protect HCPs against airborne transmission.
- Respiratory protective equipment is highly recommended when the risk of aerosol exposure is high.
- Air-purifying respirators are the best option for the HCPs during aerosol-generating procedures. Even though all air-purifying respirators can protect HCPs against aerosols, it is noteworthy that non-powered air-purifying respirators require a "respirator-fit test" before usage.
- An eye shield and eye-goggles are also recommended for eye protection for HCPs who use filtering facepiece masks or partial-face elastomeric respirators.

Air-supplying respirators are specially designed systems or devices that provide clean breathing air to the wearer and isolate the wearer from the environment's atmosphere. Therefore, they have the highest respiratory safety level. However, they have limited use in medical applications (5, 16).

Air-purifying respirators are different types of masks and devices that can clean the environment's air, thereby protect the wearer from airborne hazards and infectious agents. Air-purifying respirators are widely used in medical applications particularly during the COVID-2019 pandemic.

Air-supplying Respirators

Air-supplying respirators can be used in oxygen-deficient environments or against airborne hazards (toxic fumes) and infectious agents. There are two types of air-supplying respirators: supplied-air respiratory system and self-contained breathing apparatus (Figure 1) (16).

Supplied-air Respiratory Systems

Supplied-air respiratory systems provide clean and breathable air to the wearer from an air supply through an airline. They are especially used in biosafety level 4 laboratories that deal with highly infective agents such as the Ebola virus, the Marburg virus, or the Lassa virus (17).

Self-contained Breathing Apparatus

Self-contained breathing apparatus utilize clean and breathable air from a tank that is generally carried by the wearer. These types of equipment are used by special personnel who work in oxygen-deficient environments or are exposed to highly toxic and hazardous fumes (17).

Air-purifying Respirators

Air-purifying respirators are divided into two groups according to power supply: non-powered and powered (Figure 1).

Non-powered air-purifying Respirators

Non-powered air-purifying respirators do not require any power supply. However, all wearers should undertake "respirator

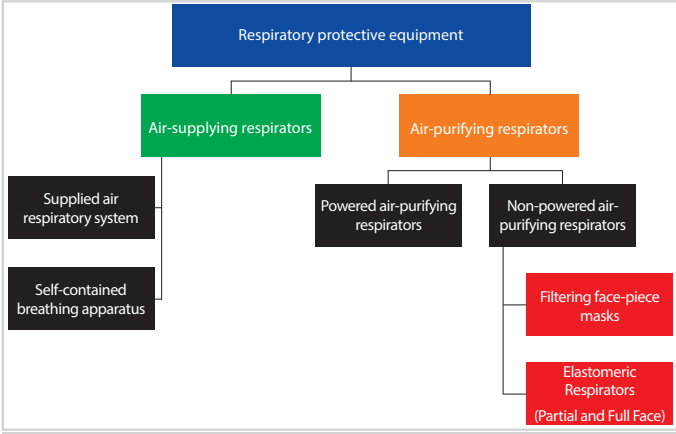

Figure 1. The classification of respiratory protective equipment

fit-testing" before usage (18). There are two types of non-powered air-purifying respirators: filtering facepiece masks and elastomeric respirators (Figure 1).

Filtering facepiece masks

Filtering facepiece masks are classified based on their filtering performance of the particles >0.3 µm as FFP1, FFP2 and FFP3. Filtering performance of FFP1, FFP2 and FFP3 can be defined as >80%, >94%, and >99%, respectively (17).

The N95 designation stands for "under test conditions" (certified under 42 CFR 84 of National Institute for Occupational Safety and Health and the United States CDC) the respirator blocks at least 95% of solid and liquid aerosol test particles. Recent studies demonstrated that FFP2 (N95 equivalent) and FFP3 (N99 equivalent) masks are highly protective against MERS, SARS, and COVID-19 when compared with surgical masks (16, 19) (Figure 2). The WHO warns that FFP2 and FFP3 masks can be effectively used up to 4 hours. All FFP2 and FFP3 masks should fit properly on to the face to create a seal.

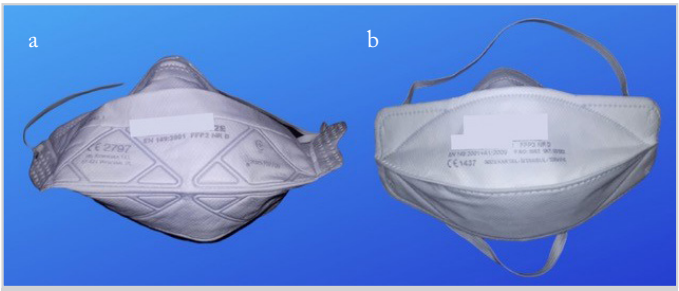

Figure 2. a, b. Filtering facepiece masks (a) FFP2 and (b) FFP3

Figure 3. a, b. Elastomeric respirators (a) partial-face, (b) full-face

Figure 4. Powered air-purifying respirator

One of the main reasons for intolerance to FFP 2 and 3 usage is breathing problems. Therefore, some FFP 2 and 3 masks may have a breathing valve (ventilation). Breathing (especially during expirium) is much easier while using FFP masks with a breathing valve. However, users may still spread droplets, even though an FFP mask with a breathing valve may effectively protect against SARS-CoV-2 transmission. Therefore, FFP masks with a breathing valve should be used attentively in healthcare settings, and anyone using an FFP mask with a breathing valve should also wear a covering surgical mask (20).

The shortage of FFP masks is a major problem worldwide. Therefore, the re-usage of disposable FFP masks is one of the hot topics during this pandemic. To date, no research or experiments have been published involving COVID-19 and FFP masks. A variety of decontamination methods have been proposed, such as UV light, hydrogen peroxide vapor, exposure to heat and steam, and leaving the mask sit for several days before reusing. The CDC provided a statement about the decontamination of FFP masks, recommending HCPs to consider using either Ultraviolet-C, vaporized hydrogen peroxide, or moist heat in crisis conditions (21-23).

Elastomeric Respirators (Partial or Full-Face)

These respirators were originally designed for pest control companies. They started to be used during surgeries or high-risk procedures during the pandemic. They have good respiratory protection and breathing is relatively easy when compared with FFP masks. They can be worn in partial or full-face (Figure 3). Despite similar respiratory protection, full-face elastomeric respirators also protect the eyes. However, poor communication quality when wearing these respirators and filter replacement are their main disadvantages (16).

Powered Air-purifying Respirator

A PAPR is defined as a respirator that filters out the contaminants in the air using a battery-operated blower to maintain clean air to the user through a tight-fitting respirator, a loose hood, or a helmet (24) (Figure 4). Powered air-purifying respirators usually have a full facepiece part and loose-fitting hoods attached to waist-mounted belt batteries. They are specific for high hazard procedures. In most PAPRs, high-efficiency particulate air (HEPA) filters are used. They can thereby filter at least 99.7% of the particles 0.3 µm in diameter (25). Moreover, the hoods of PAPRs are oil-proof and can be useful for the protection of the eyes (26).

Powered air-purifying respirators are considered more protective than the FFP masks in terms of the level of respiratory protection. The aerosol concentration inhaled by HCPs are reduced to $1/25^{th}$ in PAPRs, and $1/10^{th}$ in respirators, respectively. A systemic review with low-quality evidence demonstrated that PAPR might provide better protection in HCPs when compared with alternative respiratory protection devices. The same study also showed that satisfaction was higher concerning thermal comfort; however, lower for audibility and mobility (24). The advantages and disadvantages of FFP2/3 masks, respirators and PAPR are shown in Table 1.

Table 1. Advantages and disadvantages of FFP2/3 masks, elastomeric respirators and PAPR

	FFP2/3 mask	Elastomeric respirators (full- or partial-face)	PAPR
Assigned protection factor (respiratory protection)	10	10-25	25-1,000
Patient perspective	Hard to recognize the physician	Able to recognize the physician (better for partial face respirator)	Able to recognize the physician
Mask-fit test	Required	Not necessary	Not necessary
Face and eye protection	No (extra goggles and face shield required)	Variable (extra goggles and face shield required for partial face respirator)	Yes
Headlight usage	Possible	Possible (particularly for partial face respirators)	Not possible
Breathing discomfort	High	Intermediate	Low
Perspiration discomfort	High	Low	Low
Weight-related discomfort	No	No	Yes
Reusable	No	Yes	Yes
Filter replacement	No	Required	Required
Cleaning and Decontamination	Not recommended	Required	Required
Noise-related problem	No	No	Yes (mild to moderate)
Charging problem	No	No	Yes
Communication problem	Yes (mild to moderate)	Yes (moderate to high)	Yes (moderate to high)
Interference with occupational activities	Yes (mild)	Yes (moderate)	Yes (moderate)
Doffing and Donning	Easy	Easy	Complicated
Facial skin conditions (scar, bruise, acne)	Yes, particularly in the long term	Yes, particularly in the long term	No
Environmental pollution	High risk	Low risk	Low risk
Economic burden	Low cost	Moderate cost	Expensive

FFP2/3: filtering facepiece mask 2/3; PAPR: Powered air-purifying respirators

Respiratory Protective Equipment for Aerosol-Generating Surgical Procedures

During the COVID-19 pandemic, all otorhinolaryngology-head and neck surgeons must be cautious against aerosol-generating surgical procedures. In this section we would like to briefly review these surgical procedures in regard of the appropriate respiratory protective equipment.

Tracheotomy

In each department, a selected otorhinolaryngology-head and neck surgeon should be the primary contact person for all COVID-19 tracheotomy consultations (27). If tracheotomy is indicated for a patient with COVID-19, it is controversial whether to perform an open surgical tracheotomy or a percutaneous dilatational tracheotomy to minimize aerosol generation. In our opinion, percutaneous tracheotomy with mini-incision seems more reliable in patients with COVID-19; however, it should be decided individually. During this procedure, all HCPs should wear head cover, PAPR, gown, and gloves. Tracheotomy might be postponed for patients with COVID-19 if PAPR are not available. Properly fitting FFP2/3 masks are mandatory in case of PAPR shortage (28).

Pediatric Otorhinolaryngology Surgeries

The appropriate PPEs for a pediatric patient for a surgical intervention (peritonsillar abscess drainage, post-tonsillectomy hemorrhage, acute airway obstruction, airway or esophageal foreign body, any trauma with significant soft tissue injury or airway obstruction, complicated acute otitis media or complicated mastoiditis, nasal endoscopy for foreign body, endonasal skull base surgery for cranial neuropathies or pituitary apoplexy) is not clear (29). However, the rational approach and techniques are discussed below.

In the above-mentioned surgical procedures, cold steel instrumentation should be preferred for patients with unknown, suspected, or positive COVID-19 to reduce aerosol generation. Respiratory protective equipment must include an FFP2/3 mask, or PAPR (preferred) (29, 30).

Sinonasal Surgeries

In patients with positive COVID-19 or unknown status, the use of suction electrocautery, microdebriders, drills and balloons, should be limited to minimize the dissemination of aerosolized viral particles. Patel et al. (31) reported COVID-19 transmission to surgical staff following microdebrider use. Otorhinolaryngology-head and neck surgeons should prefer cold steel instrumentation for sinus surgeries when possible. Because of the high transmission risk, enhanced PPE, preferably PAPR, should be used for any sinonasal procedure in patients with unknown, suspected, or positive COVID-19 status (32, 33). If microde-

briders or high-speed powered instrumentations are required, the use of PAPRs is strongly recommended (34, 35).

Otologic Emergencies

Unless facial paralysis is present, tympanomastoid surgery in complicated acute mastoiditis may be postponed until COVID-19 test results are received. The use of PAPR is recommended if high-speed drills used in these procedures (29, 36). FFP2/3 masks are the second-line respiratory protective equipment.

Laryngopharyngeal Surgeries

As most laryngopharyngeal surgeries carry a high risk of aerosol generation, elective surgeries can be postponed. There are studies in the literature confirming that lasers, powered electrocautery devices, which can produce blood-containing aerosols and smoke plumes, can contain viruses and bacteria (37-39). Emergency laryngopharyngeal surgeries should be performed using PAPR or FFP2/3 masks.

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Laryngoscopic Examination During the COVID-19 Pandemic: Turkish Voice Speech and Swallowing Disorders Society and Turkish Professional Voice Society Recommendations

Quick Practice Guide

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Abstract

COVID-19 is highly transmissible and spreads rapidly in the population. This increases the occupational risk for health care workers. In otolaryngology clinic practice, patients with upper respiratory tract infection symptoms are common. Also, routine head and neck examinations such as oral cavity examination, nasal/nasopharyngeal examination, or video laryngostroboscopic evaluation are highly risky because of the aerosol formation. To emphasize this issue, two leading otolaryngology organizations in Turkey; 'Voice Speech and Swallowing Disorders Society', and 'Professional Voice Society' gathered a task force. This task force aimed to prepare a consensus report that would provide practical recommendations of the safety measurements during routine clinical care of laryngology patients. To fulfill this, universal aim, on the 2nd and 9th of May 2020, two web-based meetings were conducted by 20 expert physicians. This eighteen items list was prepared as an output.

Keywords: Laryngoscopy, endoscopic examination, COVID-19, pandemic, universal precautions

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Introduction

At the end of 2019, an infectious respiratory disease caused by severe acute respiratory coronavirus 2 syndrome (SARS-CoV2) has resulted in a worldwide health crisis known as Coronavirus disease 2019 (COVID-19). On March 11, 2020 COVID-19 was declared as a global pandemic by the World Health Organization (WHO). As of August 11, 2020, a total of 19,936,210 cases of COVID-19 in 216 countries and regions have been confirmed, and more than 700 thousand deaths were reported by that time (1).

COVID-19 is highly transmissible and spreads rapidly in the population. This increases the occupational risk for health care workers. Especially at the beginning of the pandemic, many health care workers, including otolaryngologists, were mostly

infected as a result of a lack of awareness and plans for managing infections (2). Higher rates of infection in otolaryngology have been reported in many countries (3). This higher rate of infection among otolaryngologists would be expected to be lower in the post surge era. Additionally, usage of the personal protective types of equipment will help otolaryngologists to protect themselves. In contrast, the number of patients would be expected to get higher every day with getting back to their normal clinical flow in that post-surge, pre-vaccination era.

In otolaryngology practice, patients with upper respiratory tract infection symptoms are common. Also, routine head and neck examinations such as oral cavity examination, nasal/nasopharyngeal examination, or video laryngostroboscopic evaluation are highly risky for the aerosol formation (4). Furthermore, most of the otolaryngologic examinations can be a trigger for coughing and sneezing, which are also known with aerosol generation (5).

Laryngology is one of the subspecialties of otolaryngology that focuses on voice, airway, and swallowing problems. Almost every patient with laryngological symptoms deserves laryngeal evaluation with either transoral rigid laryngoscopy or transnasal flexible laryngoscopy. Rigid transoral laryngoscopy with its high-resolution image quality is very beneficial for the examination of vocal fold mucosal lesions (6). Flexible laryngoscopy is also the gold standard examination of larynx and pharynx and is one of the most commonly performed otolaryngology procedures (7). Although in a recent study the transoral and transnasal laryngoscopy was not shown as aerosol-forming procedures, both examinations still carry the risk of a higher rate of aerosol production and laryngologists will have the burden of infection during this post-surge pre-vaccination era as well as the patients (8).

Recognizing the unprecedented challenges that we are facing or continuing the clinical care, otolaryngologists and patients have concerns about the uncertainty of measures that should be taken for safety. Until scientific advances allow for treatment or prevention for this infection disease, additional cautions should be taken by physicians and health organizations. To address that issue two of the leading otolaryngology organizations in Turkey; 'Voice Speech and Swallowing Disorders Society' and 'Professional Voice Society' gathered a task force. This task force aimed to prepare a consensus report that would provide practical recommendations of the safety measurements during routine clinical care of laryngology patients. To fulfill this aim, on the 2nd and 9th of May 2020, two web-based meetings were conducted by 20 expert physicians. And this eigtheen-item list was prepared as an output.

Main Points

- At the end of 2019, an infectious respiratory disease caused by severe acute respiratory coronavirus 2 syndrome (SARS-CoV2) has resulted in a worldwide health crisis known as Coronavirus disease 2019 (COVID-19). On March 11, 2020 COVID-19 was declared as a global pandemic by the World Health Organization (WHO).
- During COVID-19 pandemic, modifications in laryngology practice are needed due to the new clinical conditions. To enlighten this situation, considering the dynamics of our health system, Turkish Speech and Swallowing Disorders Society and Professional Voice Society members organized online meetings to prepare the following suggestions by taking into consideration of current scientific papers about 'the new normal.'
- This 18 item list would be expected to serve as recommendations for the safety of patients and physicians.

Laryngoscopic Examination During the COVID-19 Pandemic

During COVID-19 pandemic, modifications in laryngology practice are needed due to the new clinical conditions. To enlighten this situation, considering the dynamics of our health system, Turkish Speech and Swallowing Disorders Society and Professional Voice Society members organized online meetings to prepare the following suggestions by taking into the consideration of current scientific papers about 'the new normal':

1- All patients should maintain appropriate secure distance requirements in the waiting area. Consider removing and blocking off furniture in waiting areas to allow for secure distance (9, 10).
2- Maximize alcohol-based hand antiseptics vacancy and access if available. If these antiseptics are not available, encourage hand washing for staff and patients.
3- Laryngoscopic examinations should be planned carefully by taking the following precautions in cases that present hoarseness, shortness of breath, dysphagia, hemoptysis, and neck masses with unknown primary reasons (11).
4- If possible, Ear Nose Throat (ENT) examination and laryngoscopy should not be performed in the same room. The laryngoscopic examination room (LER) should have laminar airflow. If it is not available, LER should be a ventilated room. Even this is not possible, windows and doors of the room should be left open (room should be in accordance with WHO norms). If there is not such a facility, the room should be regularly and frequently ventilated (12).
5- Consider questioning the patient for possible COVID-19 symptoms before video laryngostroboscopic examinations. If possible, fever should be measured before taking the patient to the LER.

Patients who answer 'yes' to one or more of the following questions should be guided to the COVID-19 outpatient clinic (13):

· Have you had close contact with COVID-19 (+) patients?
· Have you had one of these (fever or chills, cough, sore throat, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, the recent loss of taste or smell, sore throat, congested or runny nose, nausea or vomiting, diarrhea in the past 14 days)?

6- It is mandatory using personal protective equipment (PPE) such as N95 facemasks, eyewear/face shields, cap, and gown in laryngoscopic examinations due to the higher risk of aerosol transmission (14). A health professional should al-

ways keep in mind that the most important and crucial step of the examination is using the right personal protective equipment.

7- Even in the laryngoscopic examination of patients who have been diagnosed as COVID-19 (-) regarding PCR, using N95 masks are suggested for health professionals. Hand disinfection should be provided for the patient as well as for his/her companion. Gloves and the mask should be used properly (15). Consider using double gloves, take off the top one after laryngoscopic examination properly.

8- Laryngoscopic examination can be performed either transoral with a rigid laryngoscope or transnasal with a flexible laryngoscope. Since the transoral route is thought to have more chance to produce aerosols and droplets, flexible laryngoscopy should be preferred in most of the cases (15, 16).

9- Although in voice disorders, stroboscopic evaluation is an important part of the examination, it can prolong the examination time. Not initiating stroboscopy during laryngoscopy should be exercised in appropriate cases to shorten the amount of time spent for active laryngeal examination.

10- Keeping in mind that viral particles can easily suspend in the air, consider using a topical decongestant and anesthetic patty only in necessary cases (5, 8). Aerosol sprays are not recommended. Besides, using sterile lubricant gel is suitable for flexible laryngoscopy. It shouldn't be forgotten that also the use of suction during laryngoscopy has the potential to form aerosol.

11- Minimize the laryngoscopic examination time in LER for the patient preferably <15 minutes not just for patients' health, but also for the other health care workers in the room. Also consider taking a history before the visit via phone, web portal, or telehealth to minimize the time which the patient spends in the clinic (3).

12- Consider recording all laryngoscopic examinations to avoid repeat (unless necessary) the examination of the patient (17).

13- The laryngologist who will perform the examination should practice secure distance rules during the examination, must wash hands properly (with soap and at least 20 seconds under running water), apply standard disinfection methods before and after the examination (18). Consider taking the patient to the LER alone or to allow only one accompanying person in case of necessity.

14- During transoral laryngoscopic examination, consider shifting the patient's mask upward, and consider shifting the mask downward if a transnasal examination is needed. Using a disposable otoscope tip shaped for laryngoscopy can be another alternative. Also, a modified visor can be an option for these examinations (Figure 1, 2).

Figure 1. Nasal endoscopic examination through a punctured visor (with the permission of Department of Otorhinolaryngology, Uludağ University School of Medicine)

Figure 2. Transoral endoscopic examination through a punctured visor (with the permission of Department of Otorhinolaryngology, Uludağ University School of Medicine)

15- The guideline of the Turkish Disinfection Antisepsis Sterilization Society considers 'laryngoscope' as a semi-critical device that requires high-level disinfection (18). According to this guideline, high-level disinfection ranges from gas sterilization with ethylene oxide to chemical sterilization with isopropyl alcohol, glutaraldehyde, chlorine dioxide, or orthophitaldehyde. Except for 70% isopropyl alcohol, all of these methods can be used to prevent viral transmission. Consider disinfecting not just the tip of the laryngoscope but completely (19). After the procedure, the laryngoscope should be removed from the room in a closed container to prevent contamination and fomite transmission. The health-care worker responsible for the disinfection of the tools should wash hands before and after the procedure.
16- The LER should be properly disinfected after the examination. All the surfaces that the patient or the accompany touched should be cleaned with disinfectants. It is recommended to use 2-3% hydrogen peroxide, 2-5 g/L chlorine disinfectant solutions, or 75% alcohol. According to the recommendations of the Center for Disease Control and Prevention (CDC), the time required for disinfection with isopropyl alcohol is 5 minutes, while it can take 30 minutes for disinfecting with hydrogen peroxide and other materials (20).
17- As an alternative method, consider the disinfection of LER with Ultraviolet-C (UV-C) light (UV-C lamps). However, unlike chloroquine and its variants, UV-C does not offer any residual disinfection capacity leaving supplies vulnerable to microbial contamination (21). Our knowledge of UV sterilization comes from previous MERS and SARS experience. Within the confines of distribution of ultraviolet light (10-400 nm), Ultraviolet-C (100-280 nm) has the highest disinfectant capacity (with a peak-effect wavelength of 265 nm) (22). Using a 15-watt UV-C lamp for 20 minutes will be sufficient in disinfection for rooms that are up to 30 sq. meters (23). Due to the side effects of UV-C on skin and cornea, caution signs must be placed in the room. Make sure that there is no one inside the room during disinfection with UV-C (24).
18- Considering the cleaning and disinfection time of the LER, there should be enough time between two patients that undergo laryngoscopic examination (7, 15, 17).

Conclusion

This list is far away to be complete for the prevention of the spread of the infection. With the advancements in the knowledge about disease spread and efficient techniques that can be used for prevention, changes should be considered in the future. In the meantime, this consensus report would be expected to serve as recommendations for the safety of patients and physicians.

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Acute Presentation of Undiagnosed Hereditary Angioedema of the Larynx: Averting Death

Case Report

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Abstract

Hereditary angioedema (HAE) differs from histamine-mediated angioedema in that it is resistant to steroids and antihistamines. Laryngeal attacks of this condition, if not diagnosed timely, carry a mortality rate up to 34%. Rarely, this disease goes undiagnosed until late adulthood and presents a life-threatening episode that poses a management challenge to the emergency physician. We report the case of a 48-year-old man who presented to the emergency department with progressive breathing difficulty two hours after consuming a carbonated drink. Clinical examination revealed supraglottic edema. He did not respond to steroids or antihistamines and required emergency tracheostomy to secure the airway due to failed intubation. Absence of symptoms such as itching or urticaria and inadequate response to steroids pointed to hereditary angioedema. Low complement factor 4 levels with low C1 esterase inhibitor functionality confirmed the diagnosis. This case report highlights the fact that delayed presentation of HAE can be life threatening and the diagnosis should be considered in all non-atopic adult patients with angioedema.

Keywords: Hereditary angioedema, airway obstruction, tracheotomy, C1 esterase inhibitor, airway management

Introduction

Angioedema is not difficult to diagnose for the emergency physician. Even though it can be life-threatening at times, its management is usually straightforward. Hereditary angioedema (HAE), however, is a rare entity, and relevant history might not be forthcoming in an emergency setting. Airway involvement has the propensity to become life-threatening, because unlike histamine-induced angioedema, HAE does not respond to antihistamines or corticosteroids. Upper airway symptoms are reported in 64-84% of cases (1). The attacks are usually self-limiting, even though the symptoms may take up to 72-120 hours to resolve (2). Patients with unrecognized C1 esterase inhibitor deficiency angioedema (C1-INH-HAE) who develop airway oedema have been reported to have a 15-34% mortality rate (3, 4). Availability of expert airway management teams can be the deciding factor in patient survival in such scenarios.

Case Presentation

A 48-year old gentleman presented to the emergency room with difficulty in breathing two hours after consuming a carbonated drink. He had multiple similar episodes in the past, the first being six years ago. None of these episodes required hospitalization, and symptoms would resolve over a few hours. These episodes were not associated with abdominal pain, the involvement of the extremities or genitalia. There was no history of itching, urticaria, or rash, nor were similar episodes reported among his immediate relatives.

The patient had increased work of breathing, use of accessory muscles of respiration, and a respiratory rate of 32 per minute. There was no edema of the lips or tongue. Fiberoptic laryngoscopy showed significant edema of the supraglottis (Figure 1). Hydrocortisone (200 mg) and chlorpheniramine (20 mg) were administered intravenously to re-

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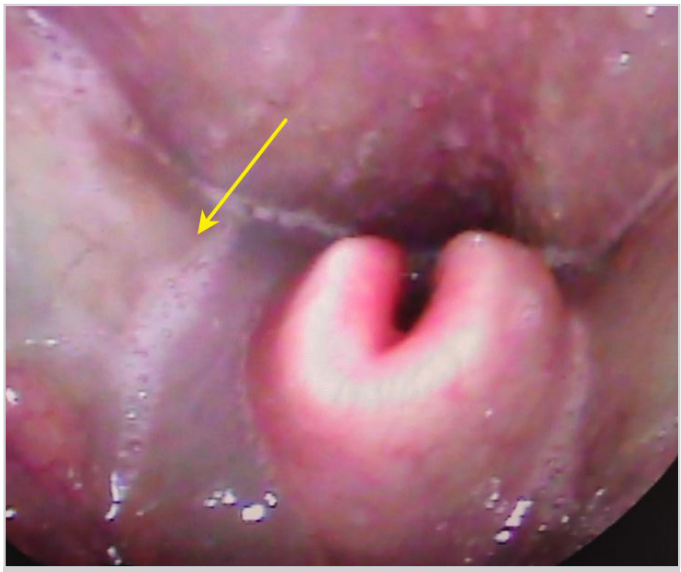

Figure 1. Laryngoscopic image showing significant edema of the aryepiglottic folds (arrow)

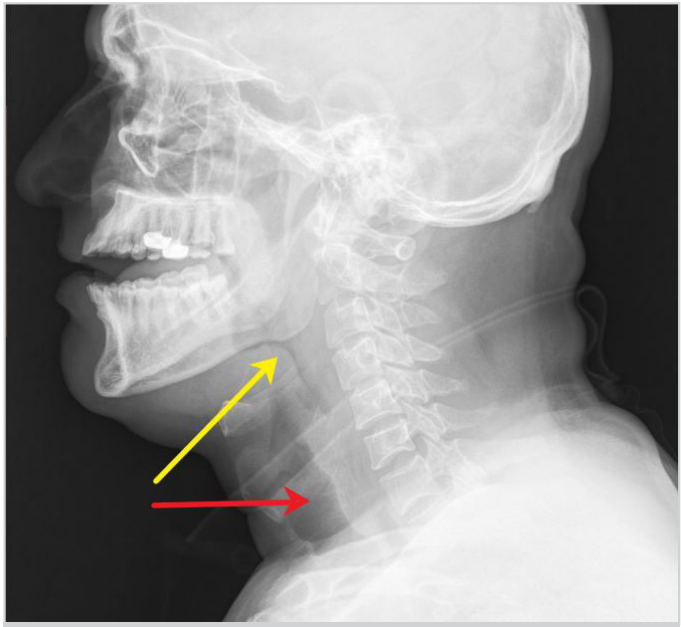

Figure 2. Lateral radiograph of the neck showing edema and narrowing of the supraglottic airway (yellow arrow) with a normal subglottis and trachea (red arrow)

duce the edema. The clinical picture was of angioedema with self-limiting similar past episodes. A lateral neck radiograph was obtained, which ruled out subglottic involvement (Figure 2). Since the patient did not respond to steroids and antihistamines, we suspected a non-atopic nature of the disease, such as HAE. Oxygen saturation showed a decreasing trend despite humidified oxygen at 5 L/hr along with nebulized adrenaline, mandating invasive airway management. Trial of intubation with tracheotomy was planned as backup, and the patient was shifted to the operation room. Fiber-optic bronchoscopy guided intubation was attempted but failed as the patient could not tolerate the procedure. A tracheotomy was done under local anesthesia in sitting posture while mask ventilating.

Main Points

- All angioedema is not histamine-mediated and might not respond to antihistamines or steroids.
- Emergency teams should have excellent airway management skills and specialist back up.
- Evaluate non-atopic patients with angioedema for hereditary angioedema.
- Screening of relatives might be useful in early detection.

Later, he was investigated for C1 esterase inhibitor (C1-INH) and complement factor 4 (C4) levels. The results were available only a couple of days later and showed C1-INH function level of 8% (normal >68%) and a C4 level of 0.07 g/L (normal: 0.14-0.54 g/L) (5).

The principal differential diagnosis was acquired angioedema (AAE). AAE can be a manifestation of underlying malignancies, especially lymphoproliferative disorders. Our patient, however, had no clinical features suggestive of this. The vast majority of HAE presents in the second decade, and report recurrent abdominal pain. AAE presents from the fourth decade onward and abdominal symptoms are rare. Both the age of onset, and the lack of abdominal pain were not in favor of HAE. However, the patient's daughter had recurrent episodes of abdominal pain for which she was hospitalized at the age of nine. Based on the presence of ascites, she was empirically prescribed antitubercular therapy at the time. Yet she continued to have intermittent symptoms. This prompted us for further investigation. Her functional C1-INH levels were 23% (normal >68%), and C4 levels were 0.07 g/L (normal: 0.14-0.54 g/L) which confirmed that we were, indeed, dealing with a case of HAE.

We did not have immediate access to C1 esterase concentrates. The airway edema subsided over the next 24 hours, and the patient was decannulated 48 hours post tracheotomy and discharged. The need for prophylactic treatment to prevent future episodes was explained. Informed consent was obtained from the patient for the publication of this report.

Discussion

Hereditary angioedema is a rare entity. Airway involvement in HAE has the propensity to become life-threatening because, unlike histamine-induced angioedema, it does not respond to antihistamines or corticosteroids. Depending upon the levels of C1-INH function, HAE is classified into three types: HAE-1 in which there is an absolute deficiency of C1-INH, HAE-2 in which only functional deficit is present, and HAE-3 where the defect is due to other mutations (6, 7).

HAE should be considered when a patient presents with recurrent angioedema without urticaria and with a family history of similar attacks. A certain grade of suspicion bears crucial significance for correct diagnosis and treatment (3). Once a clinical diagnosis of angioedema is made, tests to determine the concen-

trations of C4 and C1-INH and the latter's functional activity should be done. HAE due to C1 esterase deficiency can be diagnosed with 98% specificity when serum C4 levels are subnormal and there is low activity of C1-INH (5, 8).

The primary differential diagnosis to be excluded is AAE, which can be secondary to hematologic malignancy (9). Patients who present at an advanced age need to be investigated to rule out AAE (9, 10). The presence of B-symptoms, clinical examination, peripheral blood morphology, and immunoglobulin levels may be useful on a case to case basis (10).

The recommended medical treatment for acute episodes includes C1-INH concentrates and antagonists of bradykinin receptors (4). Newer drugs and formulations, including subcutaneous C1-INH, oral kallikrein inhibitors, and gene therapy have also been described (3). However, it has to be borne in mind that these drugs might take up to 30 minutes to act, and hence if the patient presents in distress, management of the airway might require invasive methods (11). Up to 10% of the patients with acute HAE, required tracheotomy or intubation before the diagnosis was established, according to a series (12).

All angioedema is not histamine-mediated and will not respond to antihistamines or steroids. Hence, Emergency physicians and Otolaryngology teams should have excellent airway management skills with adequate backup facilities as mortality rates associated with undiagnosed HAE are high. Patient education regarding trigger avoidance is essential as is making available prophylactic medication to these patients.

Informed Consent: Informed consent was obtained from the patient.

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Venous Ectasia of Retromandibular and Common Facial Veins: A Rare Clinical Entity

Case Report

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Abstract

Venous ectasias are benign conditions of the neck, in which focal dilatations of veins occur. Internal jugular, external jugular or superficial veins are usually the affected ones in the neck. They are often ignored or misdiagnosed. Here we are reporting a patient with venous ectasia of the retromandibular vein and the common facial vein. A 25-year-old male presented to our out-patient department with an intermittent swelling over the right side of the neck that he had for one year. The swelling was more prominent on lying down and on Valsalva maneuver. Radiologic imaging was suggestive of venous ectasia of the retromandibular vein and the common facial vein. Surgical excision was done for aesthetic reasons and in fear of thrombosis. Intraoperatively, we noticed that it was arising from the retromandibular and the common facial veins. Venous ectasias of superficial veins are rare. We can consider these patients for surgical excision in view of the risk of thrombosis, thromboembolic events, rupture, and aesthetic reasons.

Keywords: Ectasia, aneurysm, jugular vein, vein thrombosis, arteriovenous malformation, Valsalva maneuver

Introduction

Venous ectasia in the neck is a rare and benign condition. It is the dilatation or aneurysm of the venous system of the neck that may arise from the internal jugular, external jugular or superficial veins. Patients with venous ectasia present with intermittent neck swelling and rarely with pain. The etiology is mainly trauma or thoracic outlet obstruction or tumor (1). There are very few cases of venous ectasia of the common facial vein and the retromandibular vein in the literature. Here, we report a young male who presented with intermittent neck swelling which eventually turned out to be a venous ectasia of the retromandibular and the common facial veins.

Case Presentation

A twenty-five-year-old gentleman presented to our outpatient department with complaints of painless swelling over the right-side neck for one year. There was a history of increased size of the swelling while lying down and coughing as seen in Figure 1. The swelling used to disappear while sitting or in erect position. There was no history of trauma. The patient is working for the armed forces; hence, we could not rule out the probability of non-trivial injury. There was no history of fever. There was no history of dyspnea, dysphagia or change in voice.

There was no visible swelling on inspection at presentation. A diffuse swelling was more prominent over the right side neck when the patient was in right lateral position. On palpation, a diffuse, non-tender smooth-surfaced and soft swelling of 5x4 cm was palpable below the right side angle of the mandible, extending up to a middle third of the sternocleidomastoid muscle. The swelling was compressible and non-pulsatile. It was getting prominent on digital compression over the right side of the neck and during Valsalva maneuver. There was cough impulse over swelling. No other mass was palpable.

Contrast-enhanced computed tomography of the neck revealed ectatic dilatation of the venous system in the region of the retromandibular vein, near its confluence with the facial vein, forming a common facial vein as seen in Figures 2 and 3. Color doppler ultrasonography showed swirling flow with color filling and communication with the right side retromandibular vein and the common facial vein. Blood investigations including lipid profile, coagulation profile, D-dimer test and fibrinogen degradation product were done and all found normal. We considered a differential diagnosis of venous ectasia, lymphangioma and branchial cyst. Sclerotherapy was considered for this

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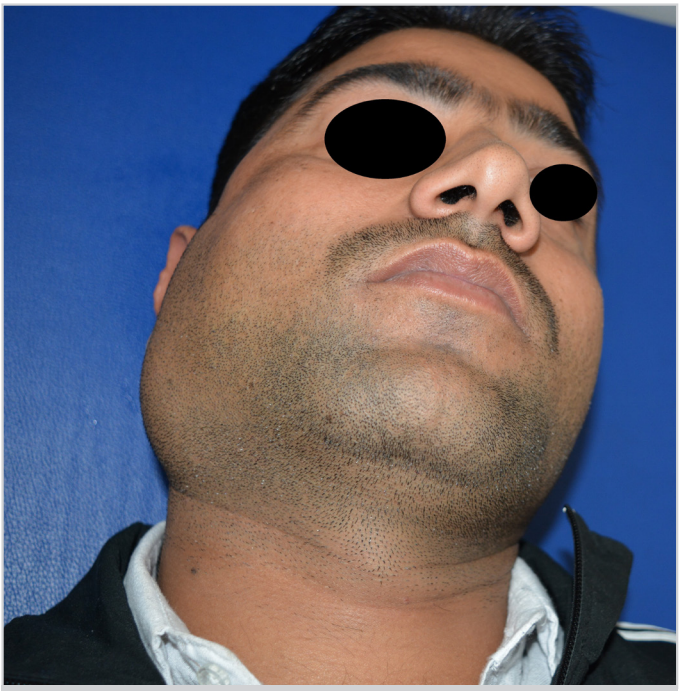

Figure 1. Prominent swelling on supine position

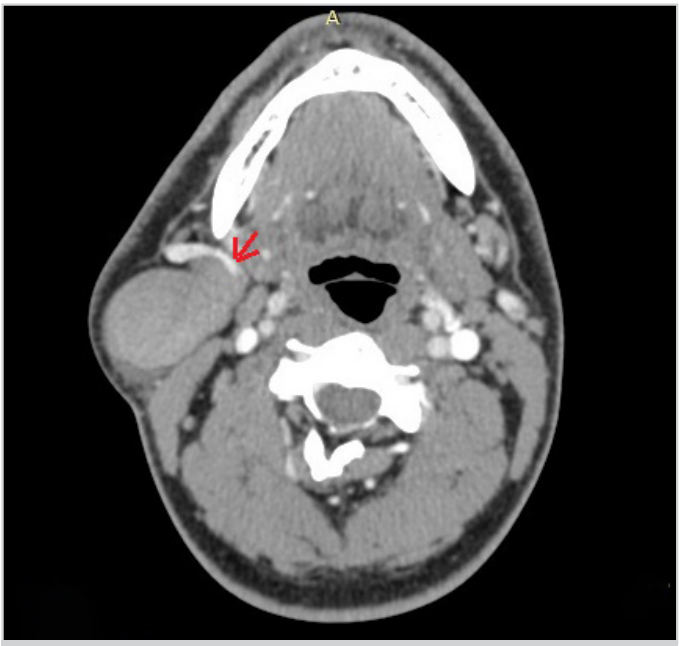

Figure 2. Axial images of the contrast enhanced computed tomography of the neck, showing venous ectasia of retromandibular vein (red arrow)

Main Points

- Venous ectasias or aneurysms are focal dilatations of the veins that are rare in the cervical region and usually misdiagnosed or ignored.
- They should be considered in the differential diagnosis of soft neck masses.
- Imaging has a key role in diagnosis.
- Conservative and surgical management have been attempted.
- Given the risk of thrombosis, thromboembolic events, rupture, and for aesthetic reasons, surgical excision is a sensible alternative.

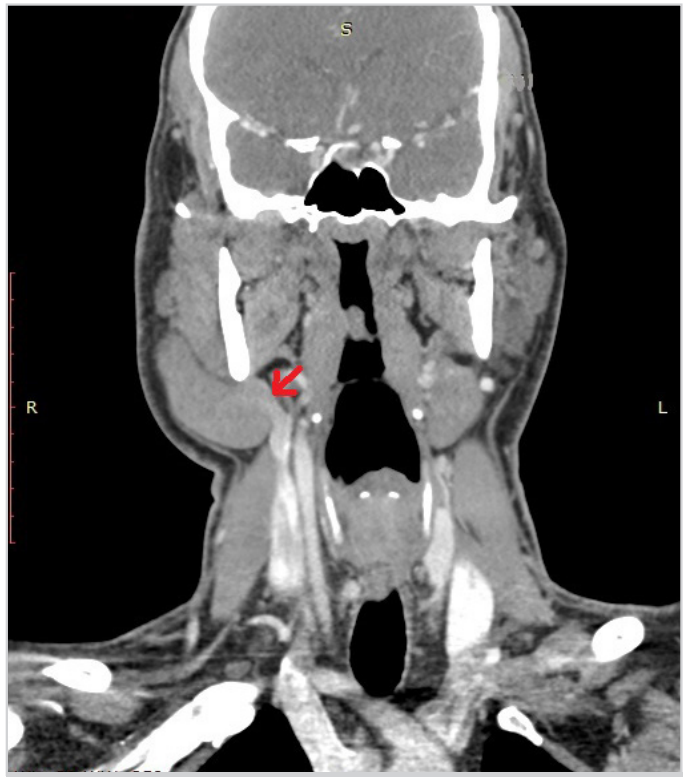

Figure 3. Coronal image of the lesion showing communication with common facial vein (red arrow)

patient; however, surgery was opted for because the lesion was directly draining into the major vein with high flow.

Excision of venous ectasia via transcervical approach was done under general anesthesia, after taking informed consent. A mass of ectatic venous channels 7x4 cm was seen at the confluence of the facial vein, anterior division of retromandibular vein and common facial vein. We ligated the common facial vein. The ectatic venous channels were adherent with the external carotid artery, which was delineated and dissected out after ligating the anterior division of retromandibular vein, the facial vein proximally and the common facial vein distally as seen in Figure 4. The excised specimen is shown in Figure 5. The patient has been on regular follow-up for two months. Informed written consent was obtained from the patient for publication.

Discussion

Venous ectasias of the retromandibular vein and the facial vein are very rare lesions. To the best of our knowledge, this is the second case report in the literature but the exact incidence could not be given due to the rarity of the lesion (2). Venous aneurysms or ectasias with focal dilatation of the vein are uncommon. The first characterization was defined in 1915, after autopsy (3). The first described venous aneurysms were in 1928 (4). Venous ectasias in the neck usually have a benign course and generally are asymptomatic. They typically present with intermittent neck swelling that may aggravate following a Valsalva maneuver.

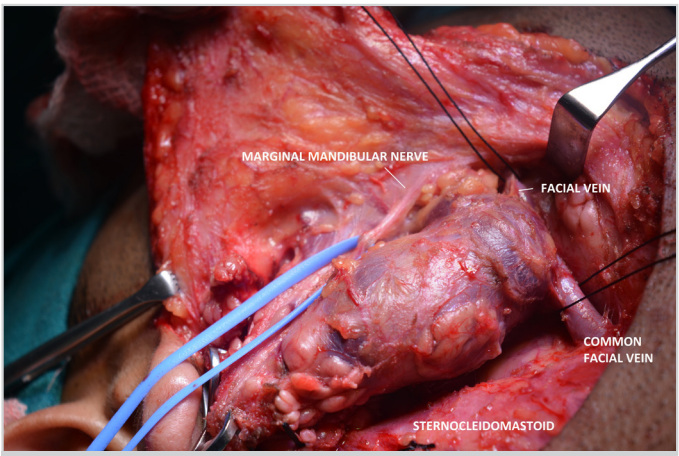

Figure 4. Intraoperative picture showing marginal mandibular nerve, facial vein and common facial vein along with lesion

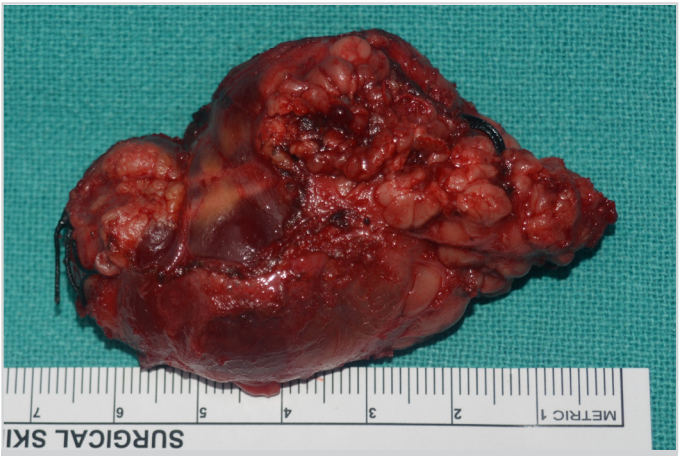

Figure 5. View of the excised specimen

Several proposed mechanisms include infection, inflammation, mechanical trauma and venous hypertension (4). Some suggested that loss of focal connective tissue components of the vein wall would be possible due to congenital underdevelopment or degenerative connective tissue loss with age (5).

Differential diagnosis includes lymphangioma, branchial cyst, cystic hygroma, cavernous hemangioma, laryngocele, pharyngeal pouch, lymph node, thyroid mass or thyroglossal duct cyst. We should do a laryngeal examination to rule out laryngocele or pharyngeal pouch. Imaging is the key to diagnosis. Doppler ultrasonography is a readily reproducible imaging technique and has an advantage of accuracy (4). Contrast-enhanced computed tomography with angiography has equal diagnostic capability for lesion evaluation, as in our case. Its main advantage is that it allows the adjacent deeper structures of the neck to be better evaluated and provides a road map for the surgeon to plan the surgery (6). In our case, magnetic resonance imaging (MRI) was done to confirm the diagnosis and rule out other possible causes. MRI provides the benefit of evaluating the nonvascular structures in the neck that may not be well visualized with ultrasonography, without exposure to radiation (7).

Management generally depends on symptoms. Both conservative and surgical management have been attempted according to the literature. In jugular venous aneurysm, there is a high chance of thrombus formation within the neck veins due to low pressure and stagnant flow. Thrombus can lead to other consequences like pulmonary thromboembolism and stroke. Patients may present with pain over swelling in such a scenario. There is a risk of rupture of venous ectasia by trauma. Cosmetics was also a concern in our patient, therefore we preferred surgical excision. Surgical removal should be considered in the management of neck for the fear of thrombosis and possible rupture risks and cosmetic/aesthetic reasons.

Endovascular embolization of aneurysm was also done in some cases (8). But embolization may lead to residual swelling over the neck. This will necessitate excision. Post-embolization lesions have poor planes. This can lead to more intraoperative complications like nerve palsies.

Venous ectasias or venous malformations should also be suspected when a patient presents with intermittent neck swelling.

Conclusion

Venous ectasia of retromandibular and common facial veins is a rare vascular pathology. Doppler ultrasonography and CT angiography are very useful in the diagnosis. Surgery can be preferred instead of embolization in cases with potential risk of complications associated with particle migration due to rapid flow of the vascular pathology.

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

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A Rare Presentation of Acquired Laryngomalacia and Tracheomalacia in a Child Associated with Apricot Sulfurization

Case Report

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Abstract

Sulfur fumigation has come to replace traditional sun drying methods for drying fruits over the years around the world as it is a cheaper and faster method because of its pesticidal and anti-bacterial properties. We report the case of an 11-year-old boy with acquired severe biphasic stridor who was exposed to extremely high concentrations of sulfur dioxide (SO2) during apricot sulfurization processes with his mother. The patient's bronchoscopy revealed severe glottic and subglottic damage. Exposure to SO2 is a health risk, particularly for individuals who are sulfide-sensitive, especially in childhood. The pulmonary epithelium may be directly injured by inhaled toxic substances at various levels of the respiratory system. To the best of our knowledge, this is the first case reported of acquired airway damage associated with sulfurization in a pediatric patient without a known history of any respiratory disease or symptoms.

Keywords: Sulfur dioxide, laryngomalacia, tracheomalacia, pediatrics, tracheotomy, pediatric otolaryngology

Introduction

Stridor is one of the physical signs of upper airway obstruction. It is a vibrating sound produced when the airway is obstructed, arising from turbulent airflow in the respiratory passages (1). Stridor can be inspiratory, expiratory or biphasic. Commonly, inspiratory stridor suggests an obstruction above the glottis owing to the collapse of soft the tissues, and expiratory stridor suggests an obstruction in the lower trachea. Biphasic stridor typically results from lesions at the level of the glottis or subglottis (2).

Inhaled toxic substances may directly damage the pulmonary epithelium at the various levels of the respiratory system. One of these substances is sulfur dioxide (SO2) which has many industrial and agricultural uses. It is a colorless toxic gas and one of the most hazardous air pollutants (3). Sulfur fumigation, which has been used for many years, has pesticide and anti-bacterial properties. It is increasingly used in place of the traditional sun drying technique for fruits and vegetables because it is cheaper, faster, and easier (4). Inhalation of high concentrations of SO2 primarily affects the upper respiratory tract and the lungs and can have immediate life-threatening effects (5). Gastrointestinal symptoms (such as nausea, vomiting and diarrhea) have been clinically reported. Most reactions to sulfites are characterized by severe dyspnea, wheezing, and bronchospasm, which can occur within minutes after exposure to materials containing sulfite (6). There is, however, limited information about the effects of sulfur fumigation on herbal safety and efficacy in children. Here we describe a male child with acquired progressive biphasic stridor who inhaled extremely high concentrations of SO2 during apricot sulfurization process.

Case Presentation

An 11-year-old male patient presented with cough, progressive respiratory distress, and noisy breathing. His complaints had begun two months earlier, and he was given several medications with the diagnosis of reactive respiratory tract disease. The patient with ever-increasing complaints became unable to sleep at night due to respiratory distress. The child's physical examination revealed dyspnea, biphasic stridor, suprasternal retractions, and rhonchi in the lung. Initially, it was learned that the child had been continuously eating ice for more than one month. A chest X-ray revealed a long segment of stenosis in the trachea (Figure 1) and neck magnetic resonance imaging (MRI) revealed diffuse edematous intense contrast enhancement in the larynx, and an edematous image compressing the trachea and stenosis at the level of the vocal cords. Bronchoscopy performed under

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general anesthesia revealed laryngomalacia and tracheomalacia. Tracheotomy was performed to relieve deteriorating respiration. The patient was given anti-reflux treatment for two months because gastro-esophageal reflux disease is strongly associated with laryngomalacia and is one of the major causes of acquired laryngomalacia. The bronchoscopy performed two months later showed no changes in the previous findings. The epiglottis was edematous and had lost its natural structure; the arytenoid cartilage was severely edematous and obstructed the respiratory tract. The glottic and the subglottic area was seen to be narrowed with 90% edema. In the bronchoscopy performed at the 6th month of the treatment, the epiglottis and the vocal cords were seen to have near-normal appearance (Figure 2). After a 1-year follow-up, the patient was decannulated and observed to be free of problems. The patient has been followed for one year without any problems.

Written informed consent was obtained from the patient's parents for publication of this case report.

Discussion

Here we report a case of an 11-year-old male child employed in apricot sulfurization with his mother. The child who did not have a medical history of prior respiratory disease or symptoms presented with cough, severe biphasic stridor and respiratory distress. His initial bronchoscopy demonstrated acquired glottic injury, laryngomalacia, and tracheomalacia with tracheal edema. Initially, it was learned that the child had been continuously eating ice for more than one month. The detailed story of the patient revealed that the child had been working in apricot production with his mother for one month. The child was reported to have inhaled extremely high concentrations of SO2 during sulfurization process that lasted about one month in Malatya. Acquired severe glottis injury associated with apricot sulfurization has not been reported before.

Exposure to SO2 is a health risk, especially for individuals sensitive to sulfide. Individuals working in the apricot sulfurization process have been reported to present with respiratory symptoms such as itchy eyes, cough, runny nose, itchy throat, shortness of breath, and decreased lung function (7). SO2 inhalation leads to acute lung inflammation and respiratory tract hyperreactivity. Moreover, it has been shown that long time inhalation of sulfur dioxide increased oxidative stress and bronchial inflammation, reduced lung function, and increased the risk of lung cancer development (8). Clinicians should consider toxic gas inhalation in every patient with respiratory problems with acute onset and which do not respond to treatment.

Main Points

- Physicians should be aware that acquired laryngomalacia and tracheomalacia in children may be due to exposure to toxic gas inhalation.
- Taking a detailed history is, as in all diseases, the most crucial approach to diagnose respiratory diseases.
- Complete and efficient evaluation and diagnosis of the stridor in children are critical for safe and timely management and intervention.

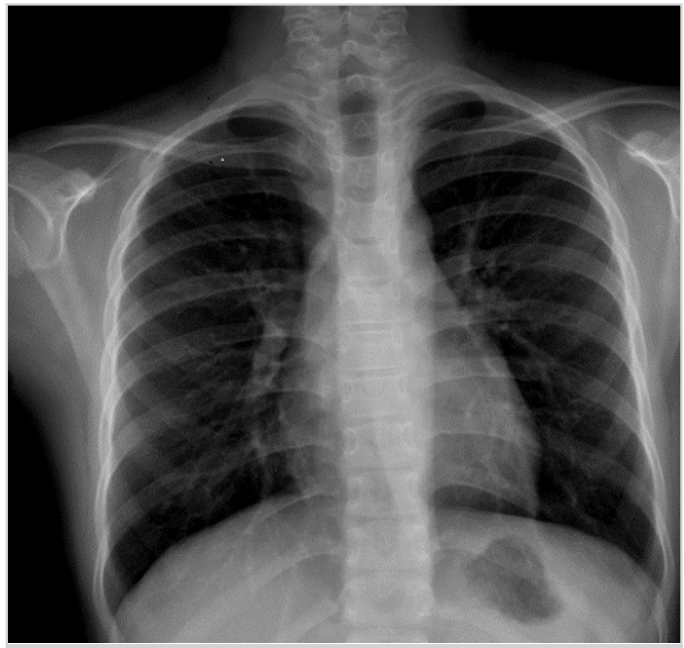

Figure 1. Chest X-ray showing a long segment of stenosis in the trachea

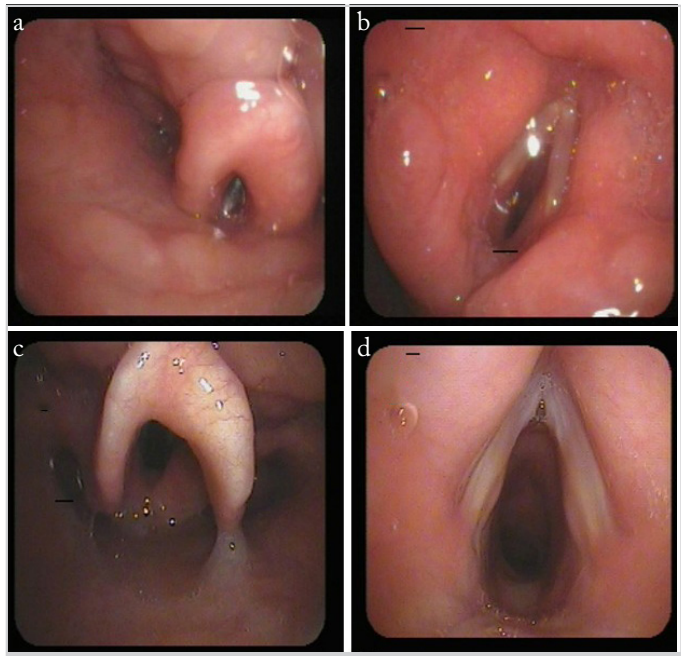

Figure 2. a-d. (a, b) Severe edema and bullous lesions in epiglottis, vocal cords and subglottic area. (c, d) Close to normal appearance on epiglottis and vocal cords after 6 months

The mechanism of SO2 damage to the lungs and the long-term results of this damage are not clear. Animal studies showed that inhalation of SO2 causes a local pulmonary inflammatory reaction and systemic effects within a few hours after exposure as an acute response (9).

Malatya, which is a city in the eastern part of Turkey, is internationally renowned as a dried apricot producing region, with

a share of 7-10% of the world's table apricots and 80-85% of dried apricots. Sulfurization of apricots is done in July each year and the process takes about 30-35 days. Individuals working in apricot sulfurization inhale SO2 gas during this process (10).

Physicians should be aware that acquired laryngomalacia and tracheomalacia in children may be due to exposure to toxic gas inhalation. Taking a detailed history is, as in all diseases, the most crucial approach to diagnose respiratory diseases. Complete and efficient evaluation and diagnosis of the stridor in children are critical for safe and timely management and intervention.

Conclusion

Apricot sulfurization workers are exposed to high concentrations of SO2. Children are more vulnerable than adults. SO2 exposure can lead to respiratory problems. Symptoms of SO2 gas inhalation injury vary and can occur immediately after exposure or have a delayed reaction, causing injury anywhere along the respiratory tract, and the exposure may lead to inflammatory changes.

Informed Consent: Written informed consent was obtained from the parents of the patient.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.V.; Materials - E.Ç.; Data Collection and/or Processing - S.U., Ö.F.Ç.; Literature Search - H.Y.; Writing - A.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.

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Surgical Planning for Cochlear Implantation in Far-Advanced Otosclerosis: The Utility of OTOPLAN

Letter to the Editor

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To the Editor,

We read with interest the recent investigation by Bajin et al. (1) that reviewed the management and treatment outcome of far-advanced otosclerosis (FAO) patients. The authors concluded that cochlear implantation (CI) represented a successful back-up option in cases of stapedotomy failure, in accordance to current findings by other authors (2-4). Bajin et al. (1) performed CI in 13 of their FAO patients (65%), with full electrode insertion in all cases and no serious post-operative complications or side effects during follow-up. Unfortunately, the authors gave no information about the type and the length of the arrays used for surgery. The appropriate choice of CI array length represents a relevant subject, as incomplete electrode insertion remains one of the main problem in CI for FAO (3).

Recently, we considered OTOPLAN (CAScination AG; Bern, Switzerland) computer program in pre-operative decision for CI in FAO patients (4). OTOPLAN is a new software for pre-operative planning in otosurgery developed by CAScination (Bern, Switzerland) in cooperation with MED-EL (Innsbruck, Austria) (5). The software, using conventional computed tomography imaging, creates reconstructed images that give a more accurate view of cochlear lumen. Additionally, OTOPLAN calculates an estimated length for every cochlear turns and provides a report with a suggested array length to use in every patient (5). In our case series of FAO patients, we disclosed a mean OTOPLAN-estimated cochlear duct length of 32.4 mm (4). Furthermore, looking at OTOPLAN reconstructed imaging, we found fibrosis located in the cochlear lumen in the middle and apical turns in two FAO subjects (4). Considering all the findings from OTOPLAN software, we decided to change surgical plans and chose a shorter electrode (24 and 28 mm instead of 31 mm) to avoid incomplete insertion (4). This software preliminarily seemed useful for the appropriate array length choice in FAO patients and should be further investigated.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.L., C.F.; Supervision - C.F.; Writing Manuscript - A.L.

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

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Author's Reply

To the Editor,

We appreciate the letter to the editor about our paper and would like to give some further details about the subject.

The difficulty of full electrode insertion in far-advanced (FAO) otosclerosis cases is a well-known phenomenon that we have discussed in our paper. In order to avoid an unpleasing surprise we always carefully evaluate high resolution computed tomography (HRCT) scans preoperatively. We develop a clear idea about mastoid cavity, middle ear and intra-cochlear anatomy. It is a must to search for decreased intra-cochlear fluid or any obstruction at round window/basal turn in COS cases which may necessitate a cochleostomy/basal turn drilling or lead to an incomplete insertion (1).

OTOPLAN is a very helpful software to reconstruct HRCT images to evaluate intra-cochlear anatomy better and indeed may facilitate the preoperative analysis (2). Although HRCT is not an ideal imaging modality to reveal fibrosis and if authors suspect intra-cochlear fibrosis in middle or apical turns, magnetic resonance imaging would have been more appropriate.

We don't prefer using Med-El flex (soft) (Med-El GmbH; Innsbruck, Austria) 31 mm electrode array in cases with less than ideal anatomies due to the risk of incomplete insertion. We prefer Cochlear Nucleus CI422 (Cochlear Corp.; Sydney, Australia) with slim straight electrode array for FAO cases and revisions. Although it has a thin and soft atraumatic electrode array, its basal stiffener helps full insertion. Its elecrode array is inserted less than 25 mm which is concordant with the suggestions of the authors of the letter to the editor.

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