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RESEARCH ARTICLE
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Effect of Controlled Hypotension by Esmolol Versus Remifentanil on Cerebral Oxygen Saturation in Patients Undergoing Endoscopic Sinus Surgery: A Randomized Clinical Trial*

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ABSTRACT

Objective: In this prospective, single blind-randomized study, we aimed to investigate the effect of controlled hypotension by esmolol vs. remifentanil on cerebral oxygen saturation (rSO2) by near-infrared spectroscopy (NIRS) in patients undergoing functional endoscopic sinus surgery (FESS).

Material and Methods: One hundred fifty patients undergoing elective FESS under controlled hypotension were evaluated for study inclusion. Group allocation was performed in a randomized fashion. Controlled hypotension was provided using continuous remifentanil (Group R) or esmolol (Group E) infusion. rSO2 was assessed during controlled hypotension by NIRS monitoring.

Demographic data, hemodynamic values, and rSO2 were recorded preoperatively, postinduction 5th min, intraoperatively (10,20,30,45,60,90 minutes), and 5 and 10 minutes after stopping hypotensive agents. The duration of surgery and anesthesia and surgeon satisfaction score were also recorded.

Results: 126 patients were included in the study. Among the demographic data, only weight was found significantly different between the groups. The unfortunate fact is that there was no significant difference in the mean of minimum rSO2(p=0.186) and also in the median of the minimum mean arterial blood pressure (MAP) (p=0.312) between Group R and Group E. Surgeon satisfaction score was significantly higher in Group R (p<0.001).

rSO2 (p<0.001, R2=0.67) was detected as the best predicting factor by the multiple regression model. While Heart rate (HR), MAP, and pre-induction rSO2 added statistically significantly to the prediction(p<0.001), the type of hypotensive drug did not (p=0.979).

Conclusion: Esmolol and remifentanil used for controlled hypotension did not cause significant rSO2 changes. Among the factors affecting rSO2 MAP, HR, and pre-induction rSO2 were detected, while the best predictor factor was pre-induction rSO2. Remifentanil provides a better surgical field than esmolol according to the VAS scale.

Keywords: Endoscopic sinus surgery, controlled hypotension, remifentanil, esmolol, monitorization

INTRODUCTION

In order to create a bloodless surgical environment and reduce blood loss, an effective hypotensive anesthesia regimen is essential during functional endoscopic sinus surgery (FESS). The goal of controlled hypotension is to maintain arterial blood pressure low enough to reduce bleeding, to provide stable hemodynamics to maintain cerebral auto-regulation unaffected during stressful surgical events. Impairment of autoregulation during controlled hypotension might increase the rate of oxygen extraction. Therefore, cerebral oxygen

*This study was registered to ClinicalTrials.gov (Registration number NCT02967029)

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saturation (rSO_2) monitorization becomes mandatory to assess cerebral oxygenation, and routine clinical evaluation of cerebral oxygenation remains a challenge.

Several studies have focused on the type of anesthetic drugs and their effect on controlled hypotension (1-5). However, the impact of hypotensive anesthesia on cerebral perfusion and oxygenation and its influence on cognitive function following surgery has not been satisfactorily described yet. Furthermore, the association between rSO_2 and controlled hypotension has not been studied in patients undergoing FESS.

Over the past decade, cerebral oxygen monitors using the near-infrared spectroscopy (NIRS) technique have been developed to evaluate cerebral perfusion by determining real-time changes in rSO_2 (6).

In our clinical routine, esmolol and remifentanil are the most frequently used agents for achieving controlled hypotension during oto-rhinological surgery. Therefore, the current prospective randomized, single-blind study aimed to investigate the effect of controlled hypotension provided by esmolol vs. remifentanil on rSO2 via utilizing NIRS in patients undergoing FESS.

MATERIAL and METHODS

Following approval from the local ethics committee (Date: 18.01.2013, No: 2), written informed consent was obtained from each participant prior to the process. This was a randomized comparative study conducted in 126 American Society of Anesthesiology (ASA) I and II adult patients aged between 18 and 65 years who were operated on for elective FESS under controlled hypotension. The current study was registered to ClinicalTrials.gov (registration number NCT02967029). Exclusion criteria included patients with hypertension, coronary artery diseases and cerebral inadequacy (documented clinically or radiologically), body mass index (BMI)> 30 kg m^{-2}, anticoagulant drug use, allergy to any of the study agents and operations shorter than 60 minutes. Patients were randomized to two groups to receive either remifentanil or esmolol to maintain the mean arterial blood pressure (MAP) between 60-65 mmHg.

After the premedication by intravenous midazolam 0.05 mg kg^{-1} 15 min before anesthesia induction, a balanced electrolyte solution of 5 ml kg^{-1} h^{-1} was initiated to all patients. Routine monitoring including electrocardiography (ECG), noninvasive blood pressure, and peripheral oxygen saturation (S_pO_2) was utilized. In addition, cerebral oxygen saturation (rSO_2) monitoring (INVOS system: Covidien, Levallois-Perret, France) was initiated prior to induction of anesthesia. An adult probe was cited in the median frontal zone as stated in the producer's instruction.

Following three minutes of tidal breathing preoxygenation, for anesthesia induction intravenous 2 mg kg^{-1} propofol, 2 µg kg^{-1} fentanyl was administered, and 0.6 mg kg^{-1} rocuronium was given to facilitate the endotracheal intubation. Ensuring the endotracheal intubation, ventilation was adjusted to keep the $PETCO_2$ at a level of 35-40 mmHg.

Anesthesia was maintained with sevoflurane (MAC set to 0.8 to 1) in a 50% oxygen-N_2O mixture. Later, as a part of the treatment regimen, either remifentanil or esmolol was administered to provide controlled hypotension at a targeted MAP value of 60 mmHg during the anesthesia period.

In group esmolol (Group E), following a loading dose of 0.5 mg kg^{-1} iv esmolol right after anesthesia induction a continuous esmolol infusion at a rate of 5-15 mg kg^{-1} min^{-1} was initiated. The maximum infusion rate is titrated to 300 µg kg^{-1} min^{-1} to maintain a target MAP of 60-65 mmHg. In group remifentanil (Group R) following a loading dose of 0.5 µg kg^{-1} iv remifentanil was administered at induction followed by a continuous remifentanil infusion rate of 0.1- 0.5 µg kg^{-1} min^{-1}. It was titrated between 0.1- 0.5 µg kg^{-1} min^{-1} to achieve a target MAP of 60-65 mmHg. No surgical stimulus was applied for 5 minutes after the initiation of the study drugs in both groups.

Baseline rSO_2 was noted just before anesthesia induction prior to additional O_2 administration. Cerebral desaturation

Table 1: Demographic data and duration of surgery

	Group R (n=63)	Group E (n=63)	P-value
Age (years)	27 (36-43)	29 (39-50)	0.073
Sex (n)			0.279
Male	33	40	
Female	30	23	
ASA (n)			0.061
I	59	51	
II	4	12	
Weight (kg)	61 (65-76.5)	67 (77-86)	<0.001
BMI (kg/m^2)	24 (23-26	26 (24-29	<0.001
Duration of operation (min)	85 (100-120)	75 (90-120)	0.093

P values show the results of Friedman test. ASA: American Society of Anesthesiologists, BMI: Body Mass Index, R: Remifentanil, E: Esmolol

was described as a decrease of rSO_2 to more than 20% of the baseline value over a period of 15 seconds and/or longer (7). If cerebral desaturation appeared, it is compensated by halving the remifentanil and esmolol infusion doses, and 250 ml bolus intravascular fluid was administrated to increase the MAP. A bolus dose of ephedrine 5 mg iv and atropine 0.1 mg kg^{-1} iv were administered to treat hypotension below the target MAP and bradycardia (heart rate (HR) ≤ 45 beats min^{-1} lasting longer than one minute, respectively. To provide coherence in the prediction of the surgical field, each operation was performed by the same specialist surgeon.

Although the anesthesiologist was not blind to the treatment allocation, the surgeon and patients were blind. The surgeon's surgical site satisfaction was measured via an 11-point scale (0= no bleeding, virtually bloodless field; 10= uncontrolled bleeding). The surgeon scored the surgical site in terms of blood loss and dryness 10 minutes after achieving the target MAP of 60-65 mmHg.

Hemodynamic data (Diastolic blood pressure (DBP), MAP, systolic blood pressure (SBP), HR), S_pO_2 and rSO_2 were noted as a baseline value before the induction of anesthesia, following the induction of hypotensive and anesthetic agent's 5^{th} min, per operative (10^{th}, 20^{th}, 30^{th}, 45^{th}, 60^{th}), and 5 and 10 minutes after the interruption of the hypotensive drugs. In addition, the duration of surgery, duration of anesthesia time, and surgeon satisfaction score were recorded.

Statistical analysis

Power analysis for two independent group comparisons was performed in G*Power (University of Düsseldorf-Düsseldorf) to determine an adequate sample size with an alpha of 0.05, a power of 0.8, and a medium effect size (d = 0.5). Based on the assumptions above, the required sample size was calculated as 118 (59 for each group). We decided to invite 150 patients to compensate for the possible dropouts.

We compared hemodynamic measurements (HR, MAP, and rSO_2) based on the time of measurement between the remifentanil and esmolol groups. Additionally, each parameter was compared between the time intervals in the groups separately. We also investigated the differences in demographic data (mentioned above), duration of surgery, minimum MAP, minimum rSO_2, and surgeon satisfaction scores between the groups.

Shapiro-Wilk test was performed for normality; data were analyzed as mean (standard deviation) for each parameter with a normally distributed and as median (first to third quartile) for each parameter without a normally distributed data. Mann-Whitney U test and independent t-test were used for intragroup comparisons. Friedman test was performed for intergroup analysis. A chi-square test of homogeneity was performed for categorical variables. A pairwise comparison was performed with a Bonferroni correction for multiple comparisons. In addition, we investigated the relative contribution of some parameters (the type of the hypotensive drug, HR, MAP, and pre-induction rSO_2) to the variation in rSO_2 during operation. A multiple regression was run. The statistically significant difference of the test was $P < 0.05$.

RESULTS

In the study, 150 patients aged between 18-65 years undergoing FESS were invited to study and assessed for study eligibility. Among them, four patients refused study participation. Fourteen patients were excluded because their operation times were shorter than 60 minutes. Six patients were not eligible due to persistent hypertension: four of them were in Group R [4/63 (6%)], and two of them were in Group E [2/63(3%)]. The data of these patients were not further

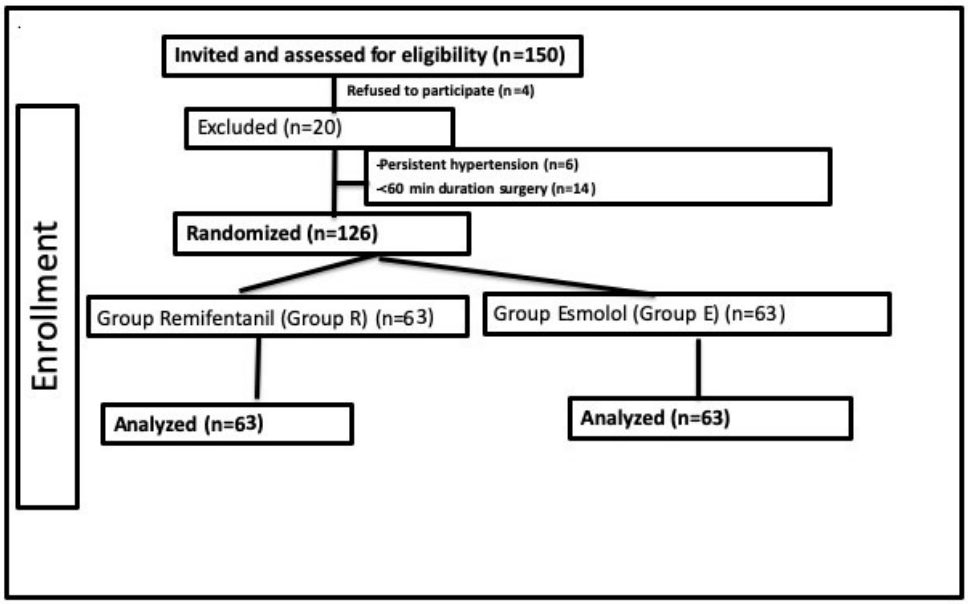

Figure 1: Study of flow diagram

Table 2: Comparison of hemodynamics based on the time of measurement between and within Remifentanil and Esmolol groups [a]

		Pre-ind. (basal level)	5 min. after ind.	Start of Op.	10th min.	20th min.	30th min.	45th min.	60th min.	End of Op.	P-values[+]
HR	R	87 (78-91)	77 (71-85)	73 (65-78)*	68 (63-74)*	64 (60-71)*	63 (58.5-70)*	64 (61-73)*	66 (61-72.5)*	67 (62.5-74)*	<0.001
	E	85 (80-87.5)	78 (73-80)	72 (66-77)*	67 (61-70)*	66 (61.5-69)*	64 (60-68)*	63 (59-66)*	63 (59-67)*	61 (58.5-66.5)*	<0.001
MAP	R	87 (83-91)	74 (70-77.5)	68 (65-71)*	65 (61-69)*	63 (60-66)*	63 (60.5-65)*	61 (58-63)*	64 (61-66)*	63 (61-66)*	<0.001
	E	86 (83.5-89)	77 (72-80)	71 (68-75)*	67 (63.5-71)*	67 (62-70)*	66 (63-68)*	63 (60-66)*	62 (60-65)*	63 (61-65)*	<0.001
rSO^2	R	71 (66-76)	74 (67-81)	70 (63-78.5)	68 (62.5-74)	67 (61-73.5)*	67 (65-74)*	67 (64-73)*	67 (64-74)*	67 (63-74)*	<0.001
	E	77 (71.5-84.5)	82 (79-86)*	78 (70-83.5)	73 (71-81)	73 (68-79)	72 (68-78.5)	71 (65-77)*	70 (64-77)*	69 (64-75)*	<0.001
Delta $rSO^{2\#}$	R		2 (-1 - 7)	-1 (-3 - 3)	-2 (-5 - 0)	-5 (-7 - -1)	-3 (-6 - -1)	-4 (-8 - -0.5)	-4 (-7.5 - -1.5)	-4 (-6 - -1)	
	E		3 (1 - 8)	-1 (-3 - 2)	-1 (-5 - 2.5)	-4 (-7 - 2)	-5 (-7 - 1)	-6 (-10 - -1.5)	-7 (-10 - -1)	-7 (-10 - -1)	

[a] Mann-Whitney U test was used to analyze between-subject variables. Friedman test was used to analyze within-subject variables. Data are presented as median (first to third quartile). Colored lines show where the statistically significant differences were seen between the groups. ($p<0.05$), [+]P values show the results of Friedman test, *Pairwise comparison (with Bonferroni correction) shows where the real difference is seen compared to basal level within each group, [#]Delta rSO_2 is calculated by extracting the measured level on each time from basal level. Within-subject comparing was not performed for Delta RSO_2 variable Abbreviations: ind: induction, min.: minute, Op.: Operation, HR: Hear rate, MAP: Mean arterial pressure, rSO_2: Cerebral oxygen saturation, R: Remifentanil, E: Esmolol.

Table 3: Summary of Multiple Regression Analysis

Variable	B	SE_B	Beta
Intercept	-25.406	3.021	
Type of the hypotensive drug	-0.012	0.465	-0.001
HR during operation	0.189	0.026	0.151*
MAP during operation	0.287	0.038	0.162*
Pre-induction RSO_2	0.888	0.023	0.788*

* $p<0.001$, B: Unstandardized regression coefficient, SE_B: Standard error of the coefficient, Beta: Standardized coefficient, [+]P values show the results of Friedman test, HR: Heart Rate
MAP: Mean Arterial Pressure, RSO_2: Cerebral Oxygen Saturation

used for statistical analysis. Finally, 126 patients completed the study and were analyzed (Figure 1).

There was a significant difference between the groups in weight among the demographic data (Table 1).

The significant fact in our findings is that the mean value of the lowest rSO_2 between Group R [65.70 (12.37)] and Group E [68.40 (10.29)] ($p=0.186$) was not statistically different (Figure 3). The median value of the minimum MAP was similar between Group R [60 (57-61)] and Group E [60 (57-64)] ($p= 0.312$) (Table II) (Figure 2). The surgeon was more satisfied with the surgical area in Group R [10 (9-10)] patients compared to Group E [8 (7-8)] patients ($p< 0.001$).

The multiple regression model enabled the detection of factors that had affected rSO2 during surgery and among four variables (type of the hypotensive drug, HR, MAP, and pre-induction rSO_2) pre-induction rSO_2 ($p < 0.001$, adjusted $R^2= 0.67$) was found as the best predicting factor. While HR, MAP, and pre-induction rSO_2 added statistically significantly to the prediction ($p< 0.001$), the type of hypotensive drug did not ($p=0.979$). The value of the slope coefficient for pre-induction rSO_2 was 0.89, which means that an increase in pre-induction rSO_2 of 1% is associated with an increase in rSO_2 of 0.89% during operation (Table III).

DISCUSSION

The interesting fact in the primary findings of the current study was that both esmolol and remifentanil did not cause significant rSO_2 changes during FESS surgery. Of all the factors affecting rSO_2, the best predictor was found to be pre-induction rSO_2. The others were heart rate and mean arterial blood pressure.

Finally, remifentanil has provided a better operative condition compared to esmolol according to the VAS scale assessed by the surgeon.

In the current study, the demographic profile of the patients between the groups was similar except for the patients' weight. However, this statistical significance has no clinical sense in our opinion because all drugs applied for premedication, induction, and maintenance of anesthesia were administered according to the patient's body weight.

This current study was designed to compare the most commonly used two agents for controlled hypotension and evaluate their effect on cerebral oxygenation monitored by

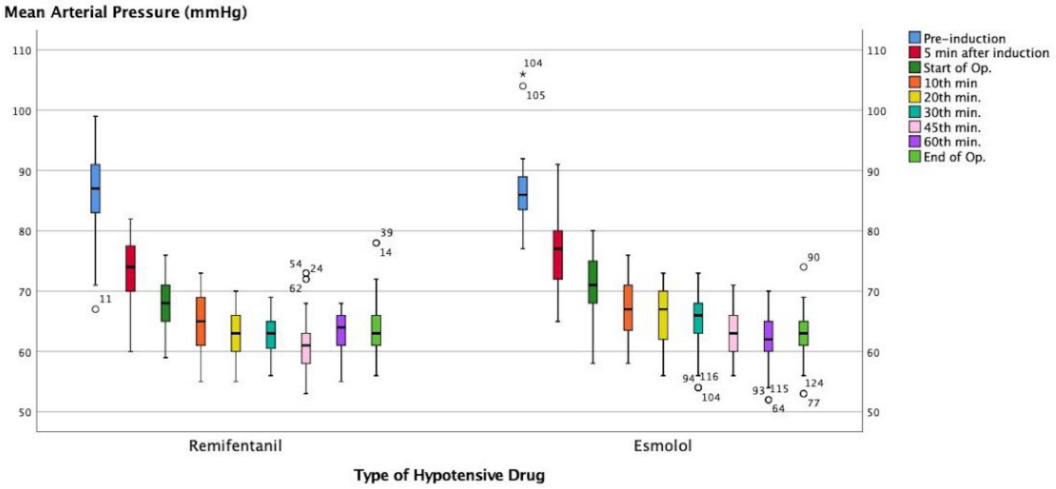

Figure 2: The analysis of mean arterial pressure based on the time of measurement between and Remifentanil and Esmolol groups.

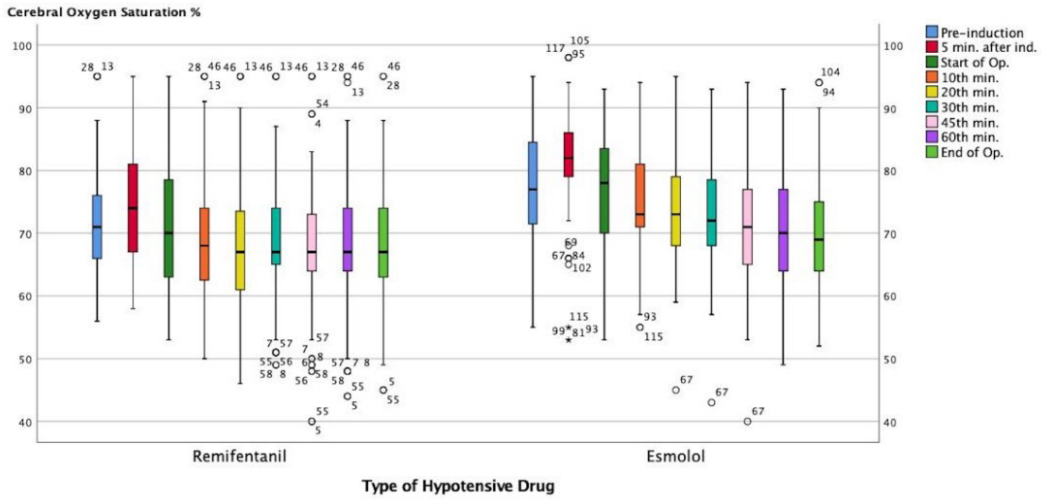

Figure 3: The analysis of cerebral oxygen saturation based on the time of measurement between and Remifentanil and Esmolol groups.

rSO_2. There are studies in the literature stating that immediate reduction in cerebral blood flow was observed when MAP was below 80 mmHg (8,9). Cerebral blood flow impairment which results in a fall on the rSO_2 may occur because MAP fall exceeds cerebral autoregulation lower boundary. In our study targeted MAP range (60-65 mmHg) was achieved with both drugs without any statistical difference. The baseline and the mean values of rSO_2 recorded throughout the study were also similar between groups. Our study shows that controlled hypotension in the FESS is reliable in terms of cerebral oxygenation, and this is similar to results of Farzanegan et al. (10). On the other hand, the agents' we used for controlled hypotension had a similar effect on mean rSO_2 without any statistically significant differences. However, the intragroup comparison has revealed that baseline rSO_2 levels in both groups were significantly different from the follow-up values, which is coherent with the literature (11-16). All mean rSO_2 levels, except the 5th minute after induction, were lower than basal levels without statistical significance. This increase at the 5th minute as was observed in a study by Farzanegan et al. may be associated with the commencement of relatively high FiO_2 exposure by preoxygenation followed by the start of mechanical ventilation (10). In addition, the study evaluated rSO_2 at each time interval. Although a statistically significant rSO_2 decrease compared to the basal level occurred at the 20th minute in group R and the 45th minute in group E this fall in rSO_2 is not clinically relevant, because the clinically meaningful cerebral desaturation was stated as reduction of 20% from baseline in different studies (17, 18).

Hemodynamic stability during hypotensive anesthesia is another important subject regarding another end-organ perfusion status beside cerebral circulation. There are numerous studies about controlled hypotensive agents in the

literature investigating this. Degoute et al concluded that the heart rate is lower, and the onset of hypotension is delayed with remifentanil in comparison with esmolol (19). Alkan et al compared esmolol, remifentanil, and nitroglycerin during controlled hypotension for FESS. They observed that the targeted MAP was reached faster, and the HR was lower with remifentanil (1). In our study, we achieved targeted MAP at the beginning of surgery and did not detect any differences between the groups in terms of mean HR and MAP.

Controlled hypotension is of paramount importance for better visualization of the surgical site, which may lead to a shorter surgery time and prevent complications in FESS. There are many reported trials assessing the influence of controlled hypotension on operative area visualization or bleeding. Although many studies showed that controlled hypotension was helpful for better surgical field or less bleeding (20-22) other results did not support the beneficial effects of controlled hypotension (23). A study investigating the effects of esmolol, remifentanil, and nitroprusside on middle ear blood flow deduced that esmolol reduced blood flow more than the others whereas remifentanil provided a better surgical field (24). This property of remifentanil as a controlled hypotensive agent has been reported (1). We found a significantly better surgical field in group R using the VAS scale which was evaluated by A senior surgeon in a single-blind manner (Group R [10 (9-10)] than Group E [8 (7-8)] ($p<0.001$)). Even though the difference was found statistically significant it may not affect the decision process regarding which agent should be preferred.

Heller et al. demonstrated a cross-correlation between $EtCO_2$ and rSO_2 but not MAP and rSO_2 (25). On the other hand, Farzanegan et al. found a cross-correlation between MAP and $EtCO_2$ with rSO_2 (10). In our study, we found a cross-correlation between MAP, HR, and pre-induction rSO_2 with rSO_2.

The study had some limitations first, there was no normotensive control group in the study, even though controlled hypotension is routinely used in almost all endoscopic sinus surgery in the absence of any contraindication. Secondly, the inhalation anesthesia technique we used may have created an effect on rSO_2. As the third, two hemispheres were not separately monitored, only one side monitoring was performed because of financial reasons. However, based on the literature, bilateral monitoring is not necessary for all procedures except for special cardiopulmonary bypass techniques such as aortic arch reconstruction or bilateral superior vena cavae operations (26).

Finally, results cannot be extrapolated to patients other than young and healthy.

CONCLUSION

Our study findings indicated that controlled hypotension provided with both esmolol and remifentanil is feasible in terms of cerebral oxygenation during endoscopic sinus surgery. We found that while the factors affecting rSO_2 were MAP, HR, and pre-induction rSO_2, it was determined that drugs did not affect rSO2, and the most important factor on rSO_2 during the operation was pre-induction rSO_2.

Although the results between the groups were similar, remifentanil provided a better surgical field than esmolol according to our evaluation with the VAS scale.

Ethics Committee Approval: This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 18.01.2013, No: 2).

Informed Consent: Written informed consent was obtained.

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Author Contributions: Conception/Design of Study- D.A., E.Ç., S.Ü.; Data Acquisition- S.Ü., L.A., Ö.T.; Data Analysis/Interpretation- L.A., H.K., Ö.T.; Drafting Manuscript- D.A., E.Ç.; Critical Revision of Manuscript- D.A., E.Ç.; Final Approval and Accountability- D.A., E.Ç.; Material or Technical Support- S.Ü., D.A., Ö.T.; Supervision- E.Ç., D.A.

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

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Evaluation of Possible Alterations in The Auditory Evoked and Event-Related Potentials in Patients with Tinnitus

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ABSTRACT

Objective: Tinnitus is a very common health problem and is reported in all age groups. The ability to objectively assess tinnitus complaints could provide significant benefits to treat or prevent its progress. In this study, we aimed to identify reliable electrophysiological biomarkers for tinnitus comparing by auditory evoked potential (AEPs), auditory event related potentials (AERPs), and mismatch negativity (MMN) responses between patients with tinnitus and healthy controls.
Materials and Methods: This study included ten subjects with tinnitus and ten age and sex-matched healthy controls. All participants gave informed consent forms and were evaluated through basic audiology evaluation, the Tinnitus Handicap Inventory for a structured diagnostic interview and tinnitus severity, and electrophysiological tests. Electrophysiological data were collected from 32 surface scalp electrodes using different frequencies of stimulus for AEPs and the oddball paradigm for AERPs and MMN.
Results: The components of AEPs for auditory stimulus with different frequencies, the components of AERPs for standard (StbD) and deviant (Dev) tones, and the difference wave (MMN) were compared between the two groups. Neither AEPs components in auditory stimulus with different frequencies, nor the AERPs components for StbD and Dev tones were affected by tinnitus ($p>0.05$ for all comparisons). However, the MMN amplitude was significantly decreased in the tinnitus group compared to the control group on the left front ($p<0.001$), right front ($p<0.01$), and left back ($p<0.01$) brain regions, while no significant changes were observed in MMN latency between the two groups.
Conclusion: Our results indicate that tinnitus leads to a deficit in the neural networks of the auditory sensory memory, and the MMN amplitude may serve as an objective biomarker for assessing tinnitus.
Keywords: Tinnitus, auditory sensory processing, evoked and event-related potentials, MMN

INTRODUCTION

Tinnitus is generally defined as the perception of various sounds in the absence of an exogenous sound source (1). Tinnitus may be an indication of auditory damage that may be accompanied by hearing loss and vertigo, and may occur even in the absence of clinical symptoms such as hearing loss. In addition, an increased neuronal activity at diverse parts of the auditory pathway may also trigger tinnitus. Studies show that tinnitus is observed in approximately 20-30% of the world's population, but only a minority of cases seek medical attention (2). Although it was widely accepted that tinnitus was caused by the degeneration of cochlear hair cells and/or auditory nerve until the 2000s, today there are studies with conflicting results and the pathophysiological events underlying tinnitus have not yet been fully explained. Recent studies show that besides acoustic trauma, depression and long-term exposure to a stressful environment can also be effective in triggering tinnitus (3). Additionally, it has been reported in the literature that there is a relationship between tinnitus and changes in cognitive functions (4). Based on these findings, it could be said that the peripheral auditory system is not the only source of tinnitus, but the central auditory system may also play an important role in the development of tinnitus.

The electrical signals produced after the mechanoelectrical cycle are transmitted to the brain via the auditory nerve and are perceived as sound after being processed here. Time-locked responses to the auditory stimuli occur in the brain, which can be recorded via disc electrodes placed on the scalp (5, 6). We

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think that these responses of the nervous system to auditory stimuli, also called auditory evoked and/or auditory event-related potentials (AEP and AERP, respectively), may provide a great advantage to examine possible changes that may occur at the cortex level in individuals with tinnitus. For this reason, in our planned study, AEPs were recorded in individuals with tinnitus using auditory stimuli consisting of 7 different frequencies, 0.25, 0.50, 1.00, 2.00, 4.00, 6.00, and 8.00 kHz, at a constant 85 dB sound intensity. And also, we recorded the AERPs using the oddball paradigm. By comparing the auditory evoked and auditory event-related potentials obtained from the age-matched control group without any hearing problems and individuals with tinnitus and normal hearing, we tried to define possible electrophysiological changes that may have occurred at the cortex level.

MATERIALS AND METHODS

Subjects

This study was conducted at the Akdeniz University Medical School, Department of Biophysics, after obtaining ethical approval from the Akdeniz University Local Ethics Committee (Approval date and number: KAEK-561 and 18.08.2021).

A total of 10 patients with tinnitus (mean age = 40.8±9.86 years) and 10 healthy controls (mean age = 36.7±6.95 years) gave informed consent and participated in the study. Six men and four women participated in each group. The inclusion criteria consisted of bilateral moderate or severe tinnitus and normal audiologic presentations (hearing threshold at 0.25 – 8 kHz < 25 dB HL). All patients were interviewed using a structured diagnostic interview, and the Tinnitus Handicap Inventory (THI) was used to determine the tinnitus severity (7). In addition, the following procedures were performed on the patients; inspection of the external auditory canal using a Heine otoscope, and pure-tone air audiometry over 0.25-8 kHz frequencies to evaluate hearing levels of patients. In order to provide more homogeneous experimental groups, patients with chronic otitis media, otosclerosis, acoustic tumor, Meniere's disease, history of ear surgery and neuropsychiatric diseases were excluded from this study.

Electrophysiological Recordings and Analysis

The electroencephalography (EEG) activity was recorded with 32 Ag/AgCl electrodes mounted in an elastic cap (Easy-cap) according to the international 10–20 system, and two linked earlobe electrodes (A1 + A2) served as references. A ground electrode was also placed on the back of the left ear. All electrode impedances were less than 10 kOhm. The EEG signal was amplified (Brainamp EEG/EP Amplifier, Brain Products, Munich, Germany), band-pass filtered (0.1-250 Hz) and digitized at a 1000 Hz sampling rate (Brainvision Recorder, Brain Products, Munich, Germany).

Auditory evoked potentials (AEPs)

Auditory evoked potentials (AEPs) were recorded using stimuli of 0.25, 0.50, 1.00, 2.00, 4.00, 6.00, and 8.00 kHz at the 85 dB sound pressure level (SPL). The duration of the 85-dB tones was 50 ms, and the tones were presented through an earphone.

The AEPs data were processed in 500 ms epochs. The averaging of 80 responses was performed with Brainstorm (8), which is documented and freely available for download online under the GNU general public license. Peak latencies of the components (first positive peak P1, second positive peak P2, first negative peak N1 and second negative peak N2) were measured from the stimulus artifact to the peak in milliseconds. The amplitudes were measured as the voltage between successive peaks.

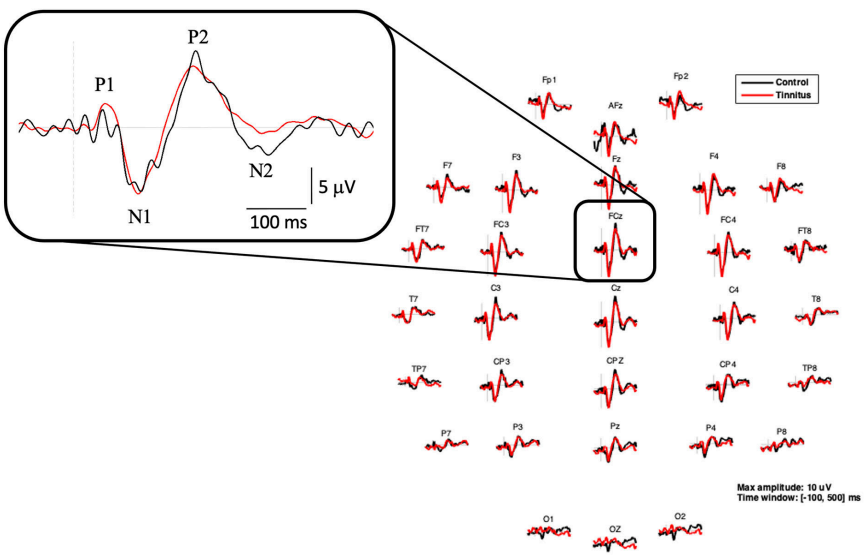

Figure 1: The grand average of AEPs evoked by 2000 Hz-auditory stimuli in the control (black) and tinnitus (red) groups. Waveforms obtained from 31 EEG channels are shown, and AEP response from FCz channel is shown in expanded format at the upper left. There are no significant differences in peak-to-peak amplitude and latency values of AEP components between groups.

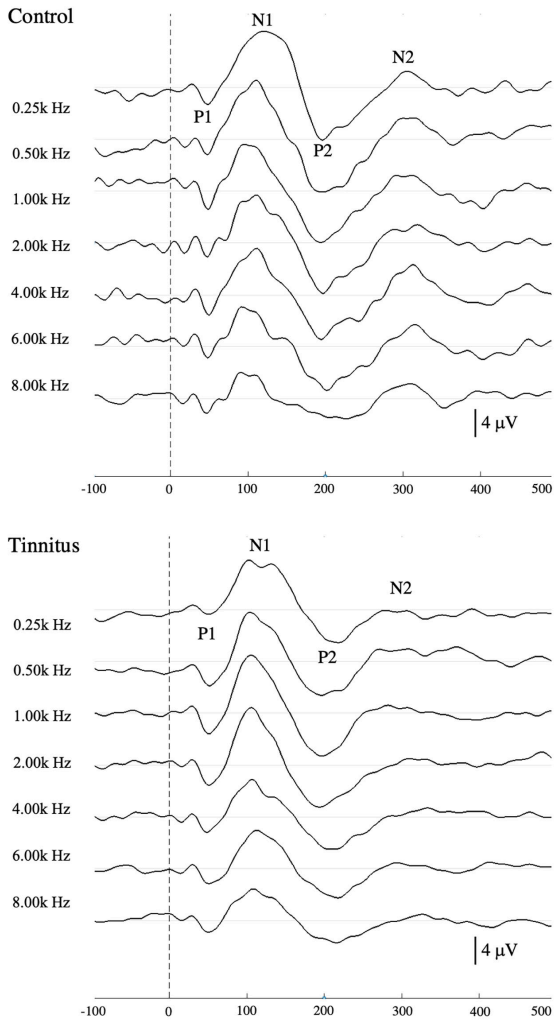

Figure 2: The grand average of AEPs in the control (top) and tinnitus (bottom) groups. Traces are prepared by averaging AEPs over F3, Fz, F4, FC3, FCz, and FC4 region evoked by 85 dB SPL stimulus at different frequencies (0.25, 0.50, 1.00, 2.00, 4.00, 6.00, and 8.00 kHz).

Auditory event-related potentials (AERPs)

Auditory event-related potentials (AERPs) were recorded using the oddball condition. In the oddball condition for auditory stimuli, frequencies of standard and deviant tones were 2000 and 2500 Hz, respectively. Deviant tones were pseudorandomized to occur at a 20% probability in a sequence of standard tones presented at the inter-stimulus interval (ISI) of 1000 ms. The tones were ordered pseudo-randomly in their series with the restriction that there were no less than two standards between consecutive deviants.

AERPs data were processed in 800 ms epochs using Brainstorm (8). AERPs were digitally filtered (0.1– 40 Hz), segmented (for each deviant and standard before deviant), and baseline corrected (-100 ms). Before the averaging procedure, the epochs with artifacts were rejected by an off-line technique. The following averaged curves were computed for each participant and then for the two groups: Standard before deviant (StbD) (AERPs to standard tones preceding deviant tones), Deviant (Dev) (AERPs to all deviant tones during the oddball paradigm) and difference wave (Dev minus StbD). Electrode positions selected as regions of interest were left front (F3, F7, FT7 and FC3), right front (F4, F8, FT8 and FC4), left back (TP7, CP3, P7 and P3), right back (TP8, CP4, P8 and P4), Fz, FCz, Cz, CPz and Pz, and mismatch negativity (MMN) amplitude and latency were calculated and averaged over these electrode positions (F, frontal; FT, fronto-temporal; FC, fronto-central; T, temporal; TP, temporo-parietal; C, central, CP, centro-parietal, P, parietal). Odd and even numbers indicate left hemisphere and right hemisphere, respectively.

Statistical Analysis

To determine the sample size for this study, we utilized the G*Power free software. The power analysis indicated that each group should have 10 participants, with a type I error level of 5% and a power of 80% to detect a minimal and significant difference between groups. The statistical analysis of the obtained data was performed with the SPSS 18.0 (SPSS, Chicago, IL, USA) software for Windows. A student t test was used to compare demographic characteristics. The peak-to-peak amplitudes and latencies of AEP components were analyzed in a Three-way mixed ANOVA including the between subject factor groups (control vs. tinnitus) and the within subject factor locations (F3, Fz, F4, FC3, FCz, and FC4 electrode regions), and stimulus (0.25, 0.50, 1.00, 2.00, 4.00, 6.00, and 8.00 kHz). The peak-to-peak amplitudes of P1, N1, P2 and N2 of AERPs were analyzed in a Three-way mixed ANOVA including the between subject factor groups (control vs. tinnitus) and the within subject factor locations (left front, right front, left back, right back, Fz, FCz, Cz, CPz and Pz) and stimulus (StbD and Dev). MMN amplitudes and latencies were analyzed in a Two-way mixed ANOVA using 2 groups (control vs. tinnitus) x 9 electrode regions (left front, right front, left back, right back, Fz, FCz, Cz, CPz and Pz). Post-hoc comparisons were analyzed with the Bonferroni test. All results are expressed as mean±standard deviation (SD). Significance levels were set at $p < 0.05$.

RESULTS

Demographics

In the present study, the age of the individuals in the tinnitus group varied between 26 and 53 years (mean age = 40.8±9.86 years), and in the control group, it varied between 24 and 47 years (mean age = 36.7±6.95 years). Sex distribution in tinnitus and control groups was 4 females and 6 males for each group. We did not observe statistically significant differences between the groups in relation to age or sex ($p>0.05$ for each condition). The tinnitus localization of the patients is bilateral, and out of the 10 tinnitus patients, 6 patients had moderate tinnitus, while the others had severe tinnitus as per the THI grading score (Grading scores of patients for THI vary between 38 and 66).

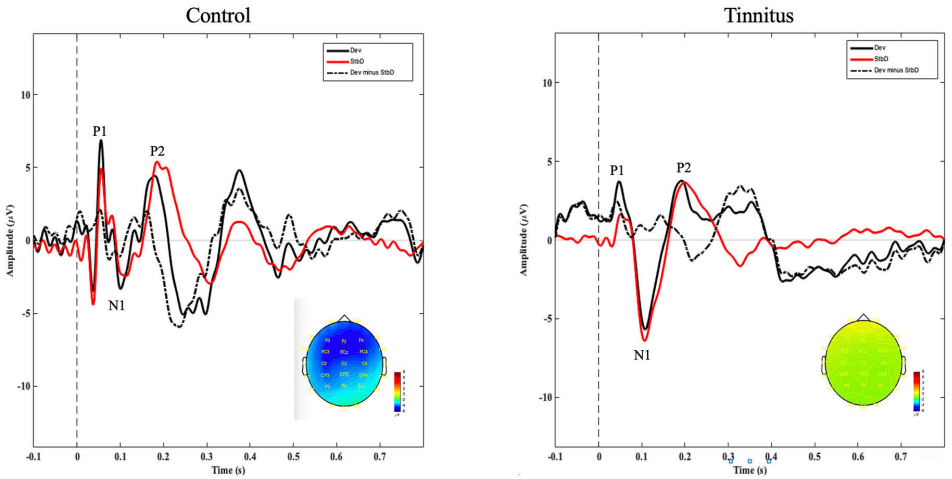

Figure 3: The grand average of auditory event related potentials (AEPs) recorded in the control and tinnitus patients. AERPs to standards (StbD, red line), deviants (Dev, black line) and difference waves (Dev minus StbD, black dash-dot line) are demonstrated for the region of interest (left front; averaged over F3, F7, FT7 and FC3). At the right bottom corner of each panel, topographies at MMN peak maximum are illustrated for each group. Difference waveforms (Dev minus StbD) were obtained by subtracting StbD responses from Dev ones and averaging across all deviation magnitudes (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

Auditory evoked potentials (AEPs)

Topographic maps of AEPs for both experimental groups are presented in Fig. 1 for 2000 Hz and the AEP traces with grand averaged over F3, Fz, F4, FC3, FCz, and FC4 electrode regions of both groups for each stimulus frequency are presented in Fig.2. Measurements were made on two negative and two positive potentials, which were seen in all of the groups. The grand average means and SD of peak latencies of AEPs components (P1, N1, P2, and N2) in F3, Fz, F4, FC3, FCz, and FC4 electrode regions of both groups are shown in Table 1. We did not observe any significant differences between groups in terms of latencies of AEP components for each stimulus condition (p>0.05), and there is no significant effect of electrode localization on the latencies of AEPs between regions of interest (p>0.05) either.

The grand average means and SD of peak-to-peak amplitude of AEPs components (P1N1, N1P2, and P2N2) in F3, Fz, F4, FC3, FCz, and FC4 electrode regions of both groups are shown in Table 2. We did not observe any significant differences between groups in terms of peak-to-peak amplitudes of AEPs for each stimulus condition (p>0.05).

Auditory event related potentials (AERPs) and MMN response

Figure 3. illustrates the components of AERPs responses to StbD and Dev tones in the oddball paradigm for both experimental groups. Difference waveforms (Dev minus StbD) obtained by subtracting StbD responses from Dev ones are also indicated in the Fig. 3. The analysis of latencies of AERPs components in response to StbD and Dev tones indicated that there is no

Table 1: The mean and standard deviations of peak latencies of AEP components in the tinnitus and control groups. There was no main group effect in terms of peak latencies of AEP components between the two groups.

	Groups	P1(ms)	N1(ms)	P2(ms)	N2(ms)	p-value
F3	Control	47.1 ±2.24	103.5±10.62	194±7.07	304.5±18.73	
	Tinnitus	51.1±4.9	109.8±14.8	206.9±24.3	306.7±31.0	
Fz	Control	46.5±2.60	104.5±9.84	194.5±6.22	3304±19.44	
	Tinnitus	51.3±4.7	108.8±14.9	207.3±24.1	206.3±31.0	
F4	Control	46.8±2.60	104±10.2	194.25±5.76	302±22.41	
	Tinnitus	50.9±5.2	109.3±15.1	207.3±24.2	307±31.0	
FC3	Control	47.75±2.49	105.6±10.2	195±4.58	304.5±18.73	> 0.05
	Tinnitus	51.1±4.9	109.8±14.2	207.3±23.3	306±30.1	
FCz	Control	46.5±2.60	104.5±9.84	195±4.58	303.5±20.17	
	Tinnitus	52.7±7.7	109.5±14	207.8±24.2	300.7±22.1	
FC4	Control	46.0±2.45	104.5±10.62	196.5±2.60	301.5±23.17	
	Tinnitus	51.9±6.3	109.8±14.8	207.3±24.1	306.3±31.2	

AEP: Auditory evoked potential; F3: left frontal; Fz: midline frontal; F4: right frontal; FC3: left fronto-central; FCz: midline fronto-central; FC4: right fronto-central

Table 2: The means and standard deviations of peak-to-peak amplitudes of AEP components in the tinnitus and control groups. There was no main group effect in terms of peak-to-peak amplitudes of AEP components between the two groups.

	Groups	P1N1(V)	N1P2(V)	P2N2(V)	p-value
F3	Control	10.97±3.52	-15.47±3.68	10.93±5.54	>0.05
	Tinnitus	9.80±2.46	-11.83±4.95	5.94±2.54	
Fz	Control	11.62±3.72	-16.60±3.91	12.52±6.90	
	Tinnitus	10.52±2.82	-13.44±15.52	7.19±2.70	
F4	Control	10.91±3.55	-14.74±3.47	10.43±5.72	
	Tinnitus	10.09±2.82	-12.57±5.35	6.22±2.60	
FC3	Control	11.10±3.54	-17.31±4.19	11.52±45.82	
	Tinnitus	9.93±2.68	-12.56±4.98	6.58±2.46	
FCz	Control	12.06±3.91	-19.52±4.96	14.88±7.86	
	Tinnitus	10.86±2.90	-15.30±5.64	8.80±3.03	
FC4	Control	11.00±3.42	-16.70±4.11	11.38±5.96	
	Tinnitus	10.01±2.85	-12.90±5.35	6.62±2.43	

AEP: Auditory evoked potential; F3: left frontal; Fz: midline frontal; F4: right frontal; FC3: left fronto-central; FCz: midline fronto-central; FC4: right fronto-central

Table 3: The mean and standard deviations of peak-to-peak amplitudes of AERP components in response to standard (StbD) and deviant (Dev) tones in the tinnitus and control groups. There was no main group effect in terms of peak-to-peak amplitudes of AERP components between the two groups.

		P1N1(V)		N1P2(V)		P2N2(V)	
	Groups	StbD	Dev	StbD	Dev	StbD	Dev
Left front	Control	7.85±2.75	8.55±2.07	7.87±2.72	8.88±4.40	6.16±4.08	7.15±3.72
	Tinnitus	6.97±1.79	8.00±2.52	8.24±2.26	7.97±2.09	4.76±1.49	6.46±1.88
Right front	Control	7.73±2.44	8.38±1.48	7.47±2.98	7.14±3.63	6.32±4.35	6.51±2.73
	Tinnitus	7.04±1.77	7.69±3.17	8.13±2.99	8.05±2.78	4.72± 1.48	7.24±2.48
Left back	Control	5.53±2.08	7.37±2.09	4.59±1.97	6.54±4.09	3.76±1.95	5.77±3.33
	Tinnitus	3.33±1.31	3.48±1.11	3.67±2.22	4.54±1.76	2.64±1.56	4.61±1.32
Right back	Control	4.35±1.72	6.15±1.68	3.98±1.95	5.39±3.74	3.93±2.00	5.65±2.92
	Tinnitus	2.75±0.92	3.55±1.29	2.99±1.70	4.41±1.63	2.12±0.96	6.66±1.61
Fz	Control	9.14±3.06	10.40±2.35	10.47±4.06	11.59±5.74	10.24±6.98	12.41±4.92
	Tinnitus	9.07±2.10	10.24±3.51	11.16±3.30	10.45±3.48	6.98±1.88	9.40±2.70
FCz	Control	8.85±3.67	9.91±2.58	11.42±4.85	13.12±7.01	11.27±7.84	13.15±5.66
	Tinnitus	9.45±2.75	10.17±4.58	11.85±3.53	11.79±4.85	7.95±1.76	10.98±3.33
Cz	Control	7.42±3.95	8.68±2.19	9.91±5.44	12.11±7.76	9.64±7.84	11.26±5.76
	Tinnitus	8.57±2.99	9.31±4.62	10.87±4.05	11.39±5.59	7.54±1.97	10.73±3.31
CPz	Control	5.92±3.54	8.20±2.79	7.57±4.94	10.04±6.90	7.19±5.59	8.61±3.62
	Tinnitus	6.42±2.43	7.44±2.98	7.88±3.75	9.21±4.68	5.85±1.85	8.96±2.43
Pz	Control	5.18±2.80	7.72±2.56	5.76±3.40	8.42±5.91	5.71±3.25	7.77±2.33
	Tinnitus	4.31±1.41	5.02±1.96	4.94±2.76	6.97±3.17	3.99±1.93	6.55±2.02

AERP: Auditory event related potential; Fz: midline frontal; FCz: midline fronto-central; Cz: midline central; CPz: centro-parietal midline; Pz: parietal midline.

statistically significant difference between groups. Mean±SD of peak-to-peak amplitudes (P1N1, N1P2, and P2N2) in response to StbD and Dev tones are shown in Table 3. When we examined the peak-to-peak amplitudes, there was a significant effect in both electrode location ($F_{2.286,132.6}$=131, p<0.001) and electrode location x group interaction ($F_{88,464}$=1.421, p<0.05). However, there is no significant group effect ($F_{711,58}$=0.66, p=0.72) for the amplitudes of AERPs.

Mean±SD of MMN amplitudes and latencies in each electrode region (left front, right front, left back, right back, Fz, FCz, Cz, CPz and Pz) are shown in Table 4. There was no main group effect ($F_{1,10}$=0.63, p=0.45) and no significant interaction of electrode region x group ($F_{8,80}$=1,13, p=0.35) on MMN latency. However, when we examined the MMN amplitudes, a significant group effect [$F_{1,22}$ = 15, p < 0.001] was observed. Post-hoc comparisons showed that MMN response was significantly decreased in the tinnitus group in comparison to the control group over regions of left front (p=0.0005), right front (p=0.008), and left back (p = 0.003). This result has indicated that the most robust decrement of MMN amplitude occurred in the left hemisphere.

Table 4: The mean and standard deviations of MMN latency and amplitude in the control and tinnitus groups. There was no main group effect in terms of MMN latency between the two groups, while statistically significant differences were observed between the two groups in terms of MMN amplitude in the left front, right front, and left-back brain regions.

	Groups	MMN Latency (ms)	MMN Amplitude (V)
Left front	Control	213.18±36.77	4.97±1.53
	Tinnitus	216.50±25.44	**2.07±0.91*** **
Right front	Control	226.83±11.51	4.18±0.88
	Tinnitus	231.83±32.97	**2.47±1.27** **
Left back	Control	225.67±26.84	5.08±1.21
	Tinnitus	231.17±31.33	**2.97±1.18** **
Right back	Control	210.17±26.18	4.09±1.25
	Tinnitus	237.33±47.20	3.91±1.46
Fz	Control	223.33±16.81	4.28±1.25
	Tinnitus	225.67±27.05	2.68±1.39
FCz	Control	220.00±20.20	3.53±1.10
	Tinnitus	224.33±26.15	3.66±1.68
Cz	Control	216.33± 23.27	4.13±1.17
	Tinnitus	223.33±27.18	3.97±1.94
CPz	Control	208.33±37.08	3.98±1.53
	Tinnitus	227.34±23.04	4.21±1.70
Pz	Control	203.00±34.38	3.80±1.38
	Tinnitus	228.67±21.30	3.45±1.64

MMN: mismatch negativity; Fz: midline frontal; FCz: midline fronto-central; Cz: midline central; CPz: centro-parietal midline; Pz: parietal midline.
Bold indicates significant differences versus Control group. For left front, ***p < 0.001; right front, **p < 0.01; and left back, ** p < 0.01.

DISCUSSION

In this study, we compared the components of auditory evoked potentials (AEPs) and auditory event-related potentials (AERPs) among individuals with tinnitus and age-matched normal individuals. We found that tinnitus has no effect on the components of AEPs. However, in this study, we observed that tinnitus has led to a significant decrement in the amplitude of mismatch negativity (MMN), but has not induced any prolongation of the MMN latency.

As known, it is possible to define that AEPs are the electrical current fluctuations in the peripheral and central nervous system in response to external auditory stimuli, and can be recorded from the scalp in a non-invasive way (9). The earlier responses of long-latency AEPs (P1, N1, P2 and N2) generally provide valuable information about the physical properties of auditory stimuli such as early sensory functions, spectral and temporal characteristics of the stimulus (10), while the later responses reflect the processing and interpretation of auditory information resulting from higher neural processes in response to the task-dependent events (11, 12). From these properties of the AEP components, several studies have highlighted that AEPs might be considered as a possible biomarker for evaluating tinnitus complaints (13, 14).

In a study, the N1-P2 peak-to-peak amplitude was specifically evaluated since it has been more reliable than the N1 and P2 analyzed independently. Researchers reported N1-P2 amplitude was highly affected by tinnitus, and also N1 latency was shorter in the tinnitus group than in the control group. In addition to this, they showed that there might be differences among different types of tinnitus. Thus, it was concluded that auditory cortical processing differed between tinnitus and normal subjects in terms of stimuli intensity-dependence (14). In contrast to this study, it has been reported that the latencies of the components N1 and P2 were higher in the tinnitus patients than in those obtained from the control group, while there were no significant changes in the N1-P2 amplitude between groups (15). In another study, it was indicated that there is a significant difference between tinnitus and control groups in terms of N1 amplitude, identifying lower amplitudes in tinnitus patients compared to control (16). In addition, researchers, investigating electrophysiological differences among tinnitus with sensorineural hearing loss, sensorineural hearing loss without tinnitus and normal individuals, have reported that the tinnitus group had a higher prevalence in auditory brainstem response abnormalities (17). These results demonstrated tinnitus complaints arise independently from hearing loss. In contrast to these studies, we also aimed to evaluate late-latency AEPs evoked by various stimuli with different frequencies (starting from 250 Hz to 8000 Hz). When we evaluated the components of AEPs for each stimulus frequency, we did not observe any significant changes in both latency and peak-to-peak amplitude of AEPs. Our results pointed that the earlier components of AEPs had not been affected by tinnitus. Therefore, from these observations, it is possible to say that tinnitus does not lead to any significant changes in the early cortical sensory processing, specifically related to stimulus frequency in our

experimental condition.

As the prevalence of tinnitus increases nowadays, it becomes a highly important topic for researchers who wish to evaluate how tinnitus affects auditory processing in higher brain function and its possible mechanisms. AEPs are generally associated with the physical properties of the stimulus and do not require a high cognitive skill. However, considering tinnitus leads to problems at the psychological and socio-professional levels, it might be inevitable for individuals with tinnitus to have a deterioration in higher cognitive functions. In this condition, the possible alterations in higher brain function could be examined by relevant methods such as event-related potentials using the oddball paradigm. In generally, P300 or MMN responses are used to evaluate higher brain functions. P300 is a cognitive ERP component reflecting voluntary attention processing (18, 19). In this context, evaluating the studies in the literature, we see that there are some variable results, showing significant delays of the P300 latency (4, 15), or no changes of the P300 component (20, 21). In the study performed by Houdayer et al. 2015, it was reported that tinnitus patients had shorter N1 and P2 latency of AERPs, but no changes in the P300 component. In addition to these findings, they also showed a reduced current density in the left inferior and parietal cortical sources of several cortical rhythms in tinnitus patients in resting state EEG (20). But, Gabr et al. 2011 reported that a significant prolongation of the P300 component was observed in the patients with tinnitus, and this prolongation is highly correlated with psychiatric evaluations conducted by using the Hamilton depression and Hamilton anxiety scales (4). In a more detailed study, researchers have investigated to ascertain any significant difference in P300 latency and amplitude between tinnitus patients and the control group. They showed a significant increase in latency and a decrease in amplitude of P300 component on increasing severity of tinnitus. However, a limitation of this study is that tinnitus patients also have sensorineural hearing loss, and therefore, it is difficult to say that the findings are only related to tinnitus (22). It is possible to explain these contradictory results by considering the P300 component requires voluntary attention, as well as may be affected by individuals' psychiatric conditions.

On the other hand, MMN is related to involuntary attention and reflects the brain capacity to discriminate the sounds in the absence of any prior instruction regardless of the individual's attentional and behavior capacity (23). Therefore, the commonly accepted mechanism for the generation of MMN response is a pre-attentive sensory memory mechanism that automatically compares present auditory input and memory traces of previous sounds. Considering these advantages, it emerges as a much better candidate than the P300 component to be a possible biomarker for objectively evaluating complaints related to tinnitus. However, few studies have investigated the possible changes of MMN response in tinnitus patients. In one of these studies, it was noted that tinnitus patients have significantly more negative N1 components for standard stimuli and have a significantly lower MMN amplitude, and the MMN latency is approximately 20 ms delayed compared to the control group, but not reached statistically significant levels, stating that MMN amplitude may become a useful biomarker to evaluate the prognosis and treatment effects of tinnitus (24). Mahmoudian et al. 2013 reported that MMN amplitude on the frontocentral regions, but not latency, was significantly affected by tinnitus (25) In another study, researchers showed that the patients with chronic tinnitus had lower the MMN amplitudes compared to the control group at the Fz region for all deviant types without affecting MMN latency and no correlation between THI and MMN responses (26). These findings indicate that the pre-attentive and automatic central auditory processing is impaired in individuals with chronic tinnitus. In contrast to these studies, El-Minawi et al. 2018 also reported tinnitus induced a significant decrement in both MMN amplitude and latency (27). On the other hand, we also evaluated the possible changes in the MMN amplitude and latency between tinnitus patients and normal healthy controls. Partly in agreement with these studies, we also determined that MMN amplitude was significantly lower in the patients with tinnitus compared to those in the control group over the left front, right front and left back electrode regions, but no significant changes were observed in the MMN latency. We can say that this decrease observed in MMN amplitude is probably due to the interaction of the sounds that tinnitus patients sense constantly and the sounds presented during the paradigm. Based on these findings, we may conclude that, while the effects of tinnitus on the early components of event-related potentials remain unclear, it has a masking effect on the MMN amplitude.

Limitation

The limitation of our study is the sample size in the patient group. Although it meets the desired power value (80%), it remains low. Further studies with a large sample size are needed to elucidate the tinnitus related alterations on AERPs with high accuracy.

CONCLUSION

Evaluation of both auditory potentials in different stimulus frequencies and auditory event-related potentials within the same study groups revealed that the alterations observed in AERPs occur independently in the physical properties of the auditory stimulus, because tinnitus does not have any effect on the components of AEP, which is mostly related to the physical properties of the stimulus, and without any requirement of high-order functioning. In addition, it is possible to say that it disturbs the neural networks of auditory discrimination and sensory memory involvement in the MMN generation, without affecting the timing of the sensory processing because no changes were observed in the MMN latency.

Ethics Committee Approval: This study was approved by Akdeniz University Local Ethics Committee (Date: 18.08.2021, No: KAEK-561).

Informed Consent: Written informed consent was obtained.

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Assessment of The Quality And Reliability of Youtube Video Content Related to the Loss of Smell

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ABSTRACT

Objective: Video-sharing sites have recently become a popular means of obtaining medical information. This study aims to analyze the English content quality and reliability of YouTube videos as a source of information on the loss of smell.
Material and Methods: A search was made on YouTube using the keyword "loss of smell," "anosmia" and "olfactory dysfunction". A total of 180 videos, 60 from each category, were reviewed. Ninety videos were excluded due to exclusion criteria, and a total of 90 videos were reviewed.
Results: Videos in 5 categories (physician-based, social/professional organizations, patients, health-related websites, and academic origins) were evaluated with DISCERN, GQS, and JAMA scores. Physician-based videos had higher scores for quality and reliability than other videos.
Conclusions: YouTube is a universal information tool growing in popularity in the medical field. Physician-based videos on the loss of smell are better in terms of quality and reliability and may be more informative.
Keywords: Anosmia, loss, olfactory, smell, video, YouTube

INTRODUCTION

The internet has revolutionized the way people access information, and the field of health is no exception. The internet is now a ubiquitous source of information for people seeking health-related information, with up to 80% of internet users seeking health information online (1). Patients and caregivers alike now have access to an array of written and visual information about diseases and treatments (2).

Google is the world's most popular search engine, and YouTube is the second most popular website globally and the most popular video-sharing platform. YouTube is increasingly being used as a source of health information by users globally (3). Unlike traditional media, YouTube provides an open platform for anyone to upload content, and it has become a hub for health-related videos. Users can upload videos on a range of health topics, including symptom management, disease prevention, and treatment options. With over 500 hours of videos uploaded every minute and over 2 billion monthly visitors, YouTube has become an essential source of information for many people (4).

However, studies have shown that many websites that provide health-related information contain inappropriate and misleading content (5). This is a concern for many health professionals, as users risk being misinformed by the information presented on YouTube. The lack of a scientific review process for uploading medical content on YouTube is a significant concern. The risk of misinformation poses a challenge to individuals seeking to understand their health issues better and can lead to wrong decisions regarding their healthcare.

The sense of smell and taste are essential for survival, as they work interconnectedly to help us perceive flavors and identify potentially dangerous substances. Therefore, any reduction in their function can significantly affect an individual's quality of life (6). Loss of smell and taste can occur due to various reasons, including aging, neurological diseases, dietary deficiencies,

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hormonal irregularities, neoplastic diseases, drug side effects, and infectious diseases (7). While around 1-2% of the global population experiences loss of smell (anosmia), only around 0.1–0.2% experience loss of taste (ageusia) (8).

With the outbreak of the coronavirus disease 2019 (COVID-19) pandemic, there has been a growing interest in the loss of smell and taste. COVID-19 patients have reported experiencing anosmia and ageusia, with 15.3% of COVID-19 patients experiencing one or both of these sensory losses, and 52% of those experiencing both (10). This has led to an increase in research articles and YouTube videos discussing anosmia and ageusia.

However, while there is a plethora of information available on the internet about the loss of smell and taste, no scientific study has been conducted on the quality and accuracy of YouTube video content related to anosmia and taste loss. With the unprecedented increase in both research articles and YouTube searches related to these sensory losses, it is important to assess the quality of information available to the public.

Therefore, there is a need for scientific studies to evaluate the accuracy and reliability of the information provided on YouTube regarding anosmia and ageusia. While the internet has become an essential source of information, individuals need to be cautious about the quality of the information they consume. It is always recommended to consult with qualified medical professionals before making any health-related decisions.

In this study, we aimed to analyze the quality and reliability of English content related to the loss of smell and taste in YouTube video content, which is used as a source of information worldwide.

MATERIAL and METHODS

The following section provides a detailed explanation of the methods used in the study to assess the quality and accuracy of YouTube videos related to the loss of smell and taste.

Ethics

This study only used publicly available data and did not involve any human subjects. Therefore, it did not require approval from the institutional review board.

Table1: Video Characteristics and Source

		Min-Max	Median	Mean±standart deviation/n-%	
Views		3.0-2166232	21495	139732±297604	
Time since upload (Day)		1.0-2957	738.5	881.3±586.6	
Duration (Second)		41.0-3525	220.0	356.5±436.5	
Comments		0.0-13000	149.5	764.7±1757.4	
Likes		0.0-32000	215.0	1934.5±4601.7	
View Ratio		16.0-288062	2311.5	21644±43497	
Origin	USA			67	74.4%
	India			6	6.7%
	UK			7	7.8%
	China			2	2.2%
	Germany			2	2.2%
	Australia			1	1.1%
	Belgium			1	1.1%
	Canada			1	1.1%
	Italy			1	1.1%
	South Africa			1	1.1%
	Turkiye			1	1.1%
Quality	Good			22	24.4%
	High			68	75.6%
Published by	Academic			10	11.1%
	Physician-based			19	21.1%
	Health-related web site			12	13.3%
	Patient			12	13.3%
	Society/Professional Organization			37	41.1%

Table 2: Correlation of the Scores of Author I and Author II

	Min-Max	Median	Mean±sd	r-p
GQS Score				
Author I	1.0-5.0	3.0	3.22±1.19	r=0.647(0.464-0.768)
Author II	1.0-5.0	2.0	2.79±1.04	p=***0.000***
DISCERN Score				
Author I	0.0-5.0	3.0	3.16±1.15	r=0.721(0.576-0.816)
Author II	0.0- .0	2.0	2.47±1.06	p=***0.000***
JAMA Score				
Author I	0.0-4.0	2.0	1.98±0.97	r=0.647(.464-0.768)
Author II	0.0-4.0	2.0	1.84±0.91	p=***0.000***

ICC: Intra Class Correlation

YouTube search

To collect data for this study, a systematic search was conducted on YouTube using the terms "loss of smell," "olfactory dysfunction," and "anosmia." The web browser's cookies and history were cleared on June 25, 2021, to ensure a fresh search. The search was conducted using the default filter "sort by relevance," which is the most commonly used filter by viewers.

Selection of videos

To ensure that the study's results are reliable and representative, only the top 60 videos for each search term were included, as previous research has shown that most viewers do not go beyond the first three pages of search results (11). Videos that were not in the English language were excluded (n=26), as English is the most commonly used language in science and is spoken in many countries worldwide. Videos without audio or video (n=3), advertisements (n=1), duplicates (n=28), irrelevant material (n=5), and conference (n=15) or lecture videos (n=12) were also excluded to ensure that only relevant and informative content was analyzed.

Analysis of videos

Two authors (OK and HSB) conducted independent analyses of the videos in this study. To evaluate the quality of information presented in the videos, the Modified DISCERN Score, Journal of the American Medical Association (JAMA) benchmark score, and Global Quality Scale (GQS) were used. The GQS is a validated quality measurement scale that utilizes a 5-point Likert scale to measure the overall quality of information and its usefulness for patients, with higher scores indicating better quality. The videos were subjectively classified into poor quality (scores of 1 or 2), intermediate quality (score of 3), and high quality (scores of 4 or 5) based on criteria proposed by Bernard et al. (12).

To evaluate the reliability of the information presented in the videos, the modified DISCERN tool and a questionnaire proposed by Singh et al. were used. The modified DISCERN tool includes five questions that are answered as either yes or no, with a maximum score of 5. The questionnaire proposed by Singh et al. evaluates the reliability of the videos based on aspects such as clear and achieved objectives, reliable sources of information, balanced and unbiased information presentation, additional sources of information listed for patient reference, and mention of areas of uncertainty (13).

The JAMA benchmark score was used to rate the online content of the videos based on authorship, attribution, disclosure, and currency, with one point given for each criterion (15).

In addition to analyzing the quality and reliability of the videos, data such as the universal resource locator (URL) information, titles, duration, origin country, time since upload, number of total views, number of likes, and uploader source were collected and saved in an Excel file. The video view ratio (VVR) was calculated to evaluate video popularity. The videos were categorized based on their uploader source, including academic institutions, society-professional organizations, physicians, health-related websites, and patients.

Statistical analysis

To analyze the data in this study, various statistical methods were utilized, including descriptive statistics such as mean, standard deviation, median, minimum, maximum, frequency, and ratio values. The distribution of variables was also examined using the Kolmogorov-Smirnov test. For the concordance analysis, intraclass correlation was employed, while the Mann-Whitney U test was used to analyze independent quantitative data. Additionally, Spearman correlation was used to examine the correlations between variables. All statistical analyses were conducted using the SPSS 28.0 software package, and the level of statistical significance was set at $p < 0.05$.

Reporting guideline

In this study, the STROBE-ME guideline was followed as a reporting method.

Table 3: Correlation between Video Characteristics and GQS,DISCERN and JAMA scores

		GQS Score	DISCERN Score	JAMA Score
DISCERN Score	r	0.646		
	p	***0.000***		
JAMA Score	r	0.619	0.666	
	p	***0.000***	***0.000***	
Views	r	0.209	0.138	0.171
	p	***0.048***	0.195	0.106
Time since upload (Day)	r	-0.275	-0.202	-0.313
	p	***0.009***	0.056	***0.003***
Duration (Seconds)	r	0.294	0.100	0.104
	p	***0.005***	0.348	0.327
Comments	r	0.164	0.077	0.106
	p	0.123	0.473	0.319
Likes	r	0.251	0.113	0.127
	p	***0.017***	0.290	0.231
View ratio	r	0.231	0.127	0.191
	p	***0.029***	0.231	0.072

Spearman correlation

RESULTS

A total of 90 videos were excluded from the study, and the remaining 90 videos were analyzed. According to the source, 19 (21.1%) of the videos were physician-based, 37 (41.1%) were social/professional organizations, 12 (13.3%) were patients, 12 (13.3%) were health-related websites, and 10 (11.1%) were of academic origins (Table 1). A significant correlation was observed between the DISCERN, GQS, and JAMA scores (Table 2). According to these scores, physician-based videos had higher scores in reliability and quality than other videos ($p < 0.01$). There was no correlation shown between image quality, country of origin, number of views, view ratio parameters, and DISCERN, GQS, and JAMA scores ($p>0.05$). A positive correlation was observed between the DISCERN, GQS, and JAMA scores (Table 3).

DISCUSSION

Loss of smell is not a common condition and affects just 1–2% of the population (8).

However, the sense of smell is of great importance to humans. The probability of patients with olfactory loss experiencing hazardous events including leaking natural gas, fire, and spoiled food has been shown to be higher in some studies (8). Since the onset of the COVID-19 pandemic, there has been a significant increase in the number of patients experiencing loss of smell. For this reason, treatment for loss of smell has become a popular topic searched on the internet.

The main finding of our study is that physician-based videos about anosmia are of higher quality and are more informative than other videos. However, the number of videos with low DISCERN, JAMA, and GQS scores was high (DISCERN: 44%, JAMA: 62%, GQS: 42%). This finding indicates that the quality of informative videos on YouTube should be improved. The first study to investigate the quality of videos on YouTube was conducted by Keelan et al. (16). In a study on rotator cuff repair videos, physician-based videos scored higher in reliability and quality (5). In another study on sarcopenia, physician-based and academic videos were found to have higher quality than other class videos (17). We also obtained similar results in this study.

YouTube is one of the world's most commonly used social media tools and allows users to like, dislike, and comment. There are many studies on the use of likes and dislikes. A study evaluating videos about retinopathy of prematurity found that useful videos had more likes and views than less useful videos (18). However, in a study by Singh et al., no relationship was found between these parameters and the usefulness of videos (19). Since independent variables such as the popularity of the channel and the number of followers affect the number of likes and dislikes, it is not an essential parameter in the reliability and quality evaluation of the video. In our study, no correlation was observed between the quality and reliability levels of the videos and the number of likes and dislikes. To the best of our knowledge, this is the first study in the literature evaluating YouTube videos on the loss of smell.

Over the past few years, social media platforms like YouTube have emerged as powerful tools for disseminating information about health and healthcare. Videos posted by healthcare professionals and patients alike can help individuals make informed decisions about their own health or that of their

loved ones. However, with so much information available, it can be difficult to determine which videos provide accurate and reliable information.

One of the biggest challenges with assessing the accuracy and reliability of health-related videos is that anyone can post a video online. Unlike traditional healthcare information sources such as medical journals or textbooks, there is no formal process for vetting the quality or accuracy of the information provided in online videos. As a result, it can be challenging to determine which videos are based on solid scientific evidence, and which are not.

Fortunately, there are a few tools that can help individuals evaluate the quality and reliability of health-related videos. One such tool is the DISCERN instrument, which was developed by a group of researchers in the United Kingdom to help people evaluate the quality of information provided in patient information materials. The tool consists of 16 questions, which cover various aspects of the information provided, including the quality of the evidence presented, the clarity of the information, and the balance of the information presented.

Another useful tool is the JAMA benchmark score, which was developed by the Journal of the American Medical Association to assess the quality of online content related to healthcare. The score assesses online content based on four criteria: authorship, attribution, disclosure, and currency. One point is given for each criterion, with a maximum score of four.

Finally, the Global Quality Scale (GQS) is a validated quality measurement scale that can be used to evaluate the quality of health-related videos. The GQS uses a five-point Likert scale to measure the overall quality of information presented in a video, with 5 representing the best quality and 1 representing poor quality.

Using these tools, healthcare professionals and patients can evaluate the quality and reliability of health-related videos posted online. By doing so, they can help ensure that individuals have access to accurate, evidence-based information about their health and healthcare options. Furthermore, by creating their own videos and sharing them online, healthcare professionals can help educate patients about their conditions and treatments, and provide them with valuable resources to help them manage their health.

Limitations

Despite its contributions to the field, this study is not without its limitations:

1. Using Google Trends to identify the most commonly used keywords may have captured only some relevant terms related to the topic.
2. Searching for videos on YouTube using different keywords may yield different results, thus potentially affecting the overall conclusions of the study.
3. This study focused exclusively on English videos, which may differ from health-related videos in other languages or regions.

Another limitation of this study is the need for a validated assessment tool to evaluate the content of the videos. Although the authors developed a content score scheme based on previous studies, the lack of a validated tool may have affected the accuracy and consistency of the evaluations. Additionally, the subjective nature of the content evaluation process may have introduced bias into the results.

Moreover, the study was limited to analyzing videos that were available on YouTube at the time of data collection. As the content on YouTube is continually changing and evolving, the results of this study may not be applicable to videos that are currently available on the platform.

Lastly, this study did not assess the impact of health-related videos on patients' health outcomes or behaviors. Future studies could investigate the potential benefits or harms of health-related videos on patients' health literacy, decision-making, and health outcomes. Despite these limitations, this study provides valuable insights into the quality and reliability of health-related videos on YouTube and highlights the need for improved regulation and quality control measures to ensure that patients have access to accurate and reliable health information online.

CONCLUSION

Video content related to health has recently become a frequently used source of information. Video content can have various sources, and it can lead to as many incorrect directions as it can be helpful. Our study on YouTube video content has shown that physician-based content is more suitable for quality and reliability. Content quality and reliability rates can be increased with supportive studies being conducted.

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Covid-19 and Bell Palsy: Could it Be Neurotrophic Involvement?

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ABSTRACT

Objective: Idiopathic cases are common, and the etiology is not clearly explained. The purpose of this study is to compare the frequency, clinical-radiological characteristics and response to the treatment of peripheral facial paralysis patients who visited the otorhinolaryngology clinic during the Covid-19 pandemic and in the same period of the previous year, and to discuss this data in the light of the literature.
Materials and Methods: Otoscopic examination findings, audiological results, application and post-healing grade information according to House Brackmann Staging system were obtained from all the patients' files. Temporal Bone Computed Tomography, which is included in the routine practice of our clinic, and Cranial & Diffusion Magnetic Resonance Imaging examinations for the elimination of central causes were applied to the patients. Facial nerve tympanic, mastoid, labyrinth segment and geniculate ganglion diameters were measured separately for the diseased side and the healthy side.
Results: In the study, Group 1 consisted of 42 patients (43%), and Group 2 consisted of 56 patients (57%). 56 (57%) of the patients were male and 42 (43%) were female. The left and right-side facial paralysis admissions were equal, but no statistically significant difference was found (p=0.068).
Conclusions: Peripheral facial paralysis is a very common case in ear, nose, and throat practice and requires priority treatment and follow-up. Since the Covid-19 virus is a new entity for the world, we think that it has a neurotrophic affinity for the facial nerve although our knowledge about this virus is limited.

Keywords: Bell palsy, COVID-19, facial nerve, radiology, steroids

INTRODUCTION

Peripheral facial paralysis (PFP) is a self-limiting disease that starts suddenly and often causes a unilateral inability to control the voluntary movement of facial muscles. Idiopathic cases are common, and the etiology is not clearly explained. Anatomical, immune, inflammatory, and ischemic mechanisms are among the most frequently emphasized reasons. In Magnetic Resonance Imaging (MRI) studies, it was reported that the facial nerve showed increased gadolinium uptake near the labyrinthine segment and geniculate ganglion during the acute phase of PFP (1,2). In addition, in histopathological and electron microscopic studies, an inflammatory reaction showing more lymphocyte infiltration, demyelination, and axonal degeneration was found in the intratemporal facial nerve (FN) in patients with acute-onset PFP (3,4). All these studies suggested that the intratemporal facial nerve was stuck in the narrow bone canal of the FN due to inflammation and edema, and as a result, it caused paralysis in the facial muscles. In addition, some studies have shown that herpes simplex virus (HSV) reactivation plays a role in the development of PFP by causing cell infiltration and demyelination through neural inflammation. For example, Bell's Palsy (BP) demonstrated HSV genomic DNA in the facial nerve of patients by polymerase chain reaction (PCR) (5,6). In animal studies, it was shown that they developed acute transient facial paralysis as a

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result of HSV inoculation into the tongue and auricles of mice, and diffuse inflammatory edema, and HSV was found in the histopathological examination of the facial nerve of these animals. It has been reported that this edema is mostly concentrated in the geniculate ganglion region (7-9).

The coronavirus outbreak that started in Wuhan province of China in December 2019 spread all over the world and created a serious pandemic. The clinical picture in Covid-19 patients constitutes a wide spectrum ranging from asymptomatic disease to multiorgan failure. Although the most prominent otorhinolaryngologic symptoms of the disease are taste and smell disorders, PFP cases have also been frequently reported. Codeluppi et al. reported that they observed more PFP cases in the emergency department in the first phase of the Covid-19 pandemic during February-May 2020 than during the same period of the previous year (7.1 and 4.1 per 100,000, respectively) and that the average age of these patients was reported to be lower than the actual one (10). Brisca et al., on the other hand, reported that there was a higher increase in pediatric PFP cases admitted to the emergency department in the same period compared to the last five years (11). Again, in this period, the publication of case reports with PFP that were Covid-19 positive in the literature revealed the idea that this virus could create a PFP clinical picture.

In this study, the demographic characteristics, radiological facial nerve segment diameters, clinical presentations, and treatment responses of the patients who visited our clinic due to PFP during the period of 10.03.2020 -10.06.2020, when the number of Covid-19 patients peaked in Turkey during the pandemic, and in the same period the previous year were evaluated comparatively. We aim to investigate whether Covid-19 has a significant effect on PFP.

MATERIALS AND METHODS

The files of the patients who applied to the Otorhinolaryngology Clinic of Adana City Research and Training Hospital between 10.03.2019-10.06.2019 and between 10.03.2020 -10.06.2020 with the diagnosis of Bell Palsy (BP) were evaluated retrospectively. 42 patients with PFP before the pandemic (Group 1) and 56 patients with PFP after the pandemic (Group 2) were included in the study. Records of patients' age, gender, PFP side, admission grade, post-healing grade, presence of additional disease, receiving steroid treatment, results of Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), and the diameters of the facial nerve tympanic-mastoid-labyrinthine-geniculate ganglion were taken from the files. Those with missing radiological examinations were excluded. Ethics committee approval was obtained for our study, and written informed consent was obtained from all patients (Date:08.07.2021, No: 984).

Otoscopic examination findings, audiological results, application, and post-healing grade information according to the House Brackmann Staging system were obtained from all the patients' files. Temporal Bone CT, which is included in the routine practice of our clinic, and Cranial & Diffusion MRI examinations for the elimination of central causes were applied to the patients. FN tympanic, mastoid, labyrinth segment diameters, and geniculate ganglion diameters were measured separately for the diseased side and the healthy side. All patients included in the study were patients with idiopathic peripheral facial paralysis.

Computed tomography was used for facial nerve (FN) segment measurements. A 128-detector Multidetector Computed Tomography (MDCT) unit (Philips Ingenuity 128, Eindhoven, The Netherlands) was used for CT imaging. The technical parameters utilized were as follows: 120 kvP, 200-400 mAs automatic tube current modulation, rotation time 0.42 s, pitch 0.6, slice thickness: 1 mm. Axial images of the temporal tomography scans were reformatted in sagittal planes.

Statistical analysis

Normal distribution control of continuous variables was evaluated with Shapiro-Wilk statistics. Variables compatible with normal distribution were examined using two independent groups t-tests to examine the differences between the groups. For the variables in a categorical structure, the Chi-Square test was used. In summary statistics, mean ± standard deviation values were given for numerical variables, while frequencies and percentages were used for categorical variables. The statistical significance level was taken as $p<0.05$. All analyses were done with IBM SPSS 22 (USA) package program trial version.

RESULTS

In the study, there were 42 patients (43%) in Group 1 before the pandemic and 56 (57%) patients in Group 2 after the pandemic. 56 (57%) of the patients were male and 42 (43%) were female. The ages of the patients were between 7 and 87, and the average age was 45. 88. There was no additional

Table 1: Diameter values in all patients

	Minimum	Maximum	Average	Standard deviation
Right labyrinthine segment (mm)	0.80	1.71	1.14	0.16
Right geniculate ganglion (mm)	0.99	2.63	1.74	0.31
Right mastoid segment (mm)	1.40	2.34	1.94	0.21
Right tympanic segment (mm)	0.70	1.62	1.10	0.23
Left labyrinthine segment (mm)	0.75	1.54	1.12	0.21
Left geniculate ganglion (mm)	1.01	2.03	1.64	0.27
Left mastoid segment (mm)	1.50	2.30	1.95	0.19
Left tympanic segment (mm)	0.75	1.42	1.08	0.19

Table 2: Grades of Bell Palsy patients at the time of admission to the hospital and facial nerve diameters on the same side of the disease

	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6	P values
Right labyrinthine segment (mm)	1.15±0.15	1.13±0.17	1.09±0.05	1.02±0.25	0.97±0.14	0.279
Right geniculate ganglion (mm)	1.78±0.33	1.71±0.29	1.68±0.25	1.84±0.08	1.50±0.48	0.542
Right mastoid segment (mm)	1.94±0.22	1.97±0.18	1.96±0.21	1.59±0.16	1.72±0.33	0.051
Right tympanic segment (mm)	1.08±0.23	1.12±0.22	1.17±0.37	0.96±0.02	1.22±0.35	0.693
Left labyrinthine segment (mm)	1.16±0.18	5.43±25.47	1.01±0.01	0.99±0.16	1.04±0.24	0.788
Left geniculate ganglion (mm)	1.64±0.27	1.66±0.26	1.68±0.20	1.62±0.12	1.50±0.48	0.878
Left mastoid segment (mm)	1.96±0.20	1.97±0.15	2.01±0.13	1.65±0.19	1.78±0.37	0.075
Left tympanic segment (mm)	1.07±0.18	1.10±0.21	1.14±0.37	0.96±0.06	1.07±0.23	0.794

Table 3: Affected side and diameters

	Effected side left	Effected side right	P values
Right labyrinthine segment (mm)	1.12±0.15	1.15±0.17	0.265
Right geniculate ganglion (mm)	1.77±0.34	1.72±0.28	0.442
Right mastoid segment (mm)	1.92±0.21	1.95±0.22	0.501
Right tympanic segment (mm)	1.07±0.21	1.13±0.25	0.161
Left labyrinthine segment (mm)	1.42±0.29	1.15±0.16	0.297
Left geniculate ganglion (mm)	1.66±0.26	1.63±0.28	0.612
Left mastoid segment (mm)	1.95±0.18	1.95±0.20	0.958
Left tympanic segment (mm)	1.08±0.20	1.08±0.19	0.990

disease in 91% of the patients. Diabetes Mellitus ranks first with 27% among patients with additional disease. The total number of right and left BP was 98: right BP was 51 in Group 1 and left BP was 47 in Group 2. In Group 1 and Group 2, the highest reference grade was grade 2 (58.5%) and then grade 3 (37.5%). All of the left BPs regressed to grade 1 and showed complete recovery. 1 of the patients with right BP regressed to grade 2; 3 of them regressed to grade 3, and all the rest showed complete recovery by regressing to grade 1. In Group 1, the post-healing grade of all the patients was grade 1. In Group 2, the post-healing grades of the patients: 1 was grade 2; 3 of them were observed as grade 3 and the remaining 52 patients were observed as grade 1. The post-healing grade of all the patients in Group 1 decreased to 1. Post-healing grades in group 2 are as follows: 52 patients - Grade 1, 1 patient - Grade 2, and 3 patients - Grade 3. 47 (48%) of the patients are right BP; 51 (52%) of them are in the form of left BP. The fact that BP is on the right or left has no effect on recovery; all the patients on the left side and 92% of them on the right side were completely grade 1 (p=0.068). Steroid treatment was given to all patients in the pre-pandemic period. (As the routine practice of our clinic, oral methylprednisolone is started at a dose of 1 mg/kg, reduced within days, and then stopped.) In the period after Covid-19, since the results of the use of steroids in the first days are not known, no steroid was given to any patient in this period. Groups and gender did not have a statistically significant effect on healing (before or after Covid-19) (p=0.534, p=0.100, respectively). There is a statistically significant difference between the post-healing grade and comorbidity (p=0.049). The probability of staying as BP grade 3 in patients with additional disease is 20%. The healing rate of those who do not have any additional disease as grade 2 or 3 is 1.1% for both. There is a statistically significant difference between the post-healing grade and the reference grade (p=0.005). The low level of the post-healing grade (improvement) is statistically and significantly associated with the low level at the first application. The average of the diameters of the facial nerve segments in all patients is given in Table 1.

There is no statistically significant difference between the hospital admission grade of BP patients and the facial nerve geniculate, labyrinth, mastoid, and tympanic segment diameters on the same side of the disease (Table 2, p> 0.05 for all segments).

Facial nerve diameters by the affected side are shown below (Table 3).

Between Group 1 and Group 2, right tympanic segment diameters (p <0.001) in the patients with right BP, left tympanic segment diameters (p=0.006) in the patients with left BP, and right geniculate ganglion diameters in the patients with right BP (p=0.014), there is a statistically significant difference in terms of variables. In Group 2, the right tympanic segment diameters are wider in the patients with right BP compared to Group 1. (p <0.001). In Group 2, left tympanic segment diameters are wider in the patients with left BP compared to Group 1. (p=0.006). In Group 1, the right geniculate ganglion diameter is larger in the patients with right BP compared to Group 2. It is wider in Group 1 (p=0.014) (Table 4).

There is a statistically significant difference between the comorbid disease groups only in terms of the left mastoid segment variable (p=0.035). In other words, the left mastoid segment diameter was found to be narrower in patients with additional disease. While there is no statistically significant relationship between comorbidity and admission grade (p=0.326), there is a statistically significant relationship between comorbidity and the post-healing grade (p=0.049).

Table 4: The FN segment diameters of the groups

	Group 1	Group 2	P Values
Right labyrinthine segment(mm)	1.17±0.11	1.11±0.19	0.052
Right geniculate ganglion (mm)	1.86±0.24	1.66±0.33	0.014
Right mastoid segment (mm)	1.98±0.20	1.90±0.22	0.821
Right tympanic segment (mm)	0.96±0.11	1.20±0.24	<0.001
Left labyrinthine segment (mm)	1.20±0.17	3.86±20.43	0.087
Left geniculate ganglion (mm)	1.69±0.26	1.61±0.27	0.691
Left mastoid segment (mm)	1.99±0.15	1.92±0.21	0.118
Left tympanic segment (mm)	0.99±0.14	1.15±0.20	0.006

Complete recovery in facial paralysis is less common in patients with comorbidities. There is no statistically significant difference in age between the post-healing grade groups (2-3-4-5-6) (p=0.052). However, the lowest mean age is grade 4, and the highest average age is grade 3.

The post-healing grade of all 42 patients who took steroids decreased to grade 1. The post-healing grades of patients not receiving steroids are grade 1 in 52 patients, grade 2 in 1 patient, and grade 3 in 3 patients. There was no statistically significant difference in the age variable between pre and post-Covid-19 groups (p=0.751). There is no significant difference in age between Group 1 and Group 2. The age distribution of patients with BP during the pandemic period is similar to the previous year.

DISCUSSION

Facial paralysis publications associated with Covid-19 in the literature are mostly in the form of case reports. The number of articles submitted to the literature for the virus considered to be neurotrophic is expected to increase in time. There are articles in the literature presenting variable data in terms of female and male distribution. According to the information obtained from the presented cases, PFP can be the first finding in Covid-19, or it can develop in the first 10 days (10-16). In addition, bilateral or unilateral PFP cases associated with Guillain-Barré syndrome (GBS) have been reported in Covid-19 patients in the literature (17-22). In our study, the pre-Covid period group is Group 1 and the post-Covid period group is Group 2. While all the patients in Group 1 took steroids, the patients in Group 2 did not take any. There is no significant statistical difference between the groups in terms of the post-healing grade. However, the number of patients in Group 2 is higher. We think that Covid-19 is a neurotropic virus and increases PFP.

Although the main cause of idiopathic PFP (Bell's Palsy) has not been fully elucidated in the literature, the detection of herpes simplex virus type 1 (HSV-1) genome in the endoneurial fluid obtained from FN in these patients is the most likely pathogenic mechanism in the geniculate ganglion and meatal foramen, and it supports the view of inflammation due to HSV-1 reactivation in the segment of the labyrinth (9-11). The mechanism of PFP formation due to Covid-19 is probably demyelination induced by an inflammatory process, as in PFP due to the neurotropic herpes viruses HSV and varicella zoster virus

Table 5: Isolated PFP cases in the Covid-19 Period

	Age	Gender	Side	Grade	Treatment	Conclusion
Wan et al.28 (2020)	65	Female	Left	4	The symptoms of left facial paralysis relieved after antiviral treatment with arbidol and ribavirin	Complete
Goh et al.29 (2020)	42	Male	Left	3	Prednisone and valacyclovir, as well as lopinavir/ritonavir in an attempt to reduce SARS-CoV-2 viral replication	Complete
Lima et al. (2020)	43*	Female	Right	3	Oral steroids	Partial
	25*	Female	Right	2	Oral steroids + acyclovir	Complete
	33	Female	Right	3	Oral steroids + acyclovir	Partial
	26	Female	Left	2	Oral steroids	Complete
	50	Female	Left	3	Oral steroids	Partial
	38	Female	Left	2	Supportive	Complete
	39	Female	Right	2	Oral steroids	Complete
	34	Female	Left	2	Intravenous steroids	Complete
Figueiredo et al. (13)	35	Female (pregnant)	sol	3	Corticosteroid therapy (10-day tapering prednisolone course, starting at 60mg/day) was initiated in order to optimize functional recovery	Partial
Mehta et al. (16)	36	Male	Right	3	prednisone and eye lubrication,	Complete

*As the first symptom of Covid-19 and the main reason for patients' admission to the hospital. PFP: Peripheral facial paralysis.

(VZV). Some authors have reported that demyelination may occur in cranial nerves due to a secondary delayed immune response as a result of Covid-19 viremia (12,14,23). In addition, the fact that Covid-19 has been associated with various neurological diseases, such as anosmia, acute ischemic stroke, encephalopathy, and GBS, indicates that this virus may cause cranial nerve involvement (24). Neurological findings have been reported in approximately 36.4% of Covid-19 (11,17). For this reason, additional symptoms should be questioned in patients presenting with isolated FPP, cranial nerve examinations should be performed, and MRI should be requested if necessary.

Correa et al. published cranial nerve (CN) (1st, 2nd, 6th, and 7th CN) abnormalities and magnetic resonance imaging (MRI) results of these patients in six Covid-19 positive cases (25). FN involvement was present in four of the six patients published. One patient had unilateral PFP, while the other had unilateral PFP and ipsilateral abducens nerve paralysis. Bilateral PFP was observed in the other two patients. One of the bilateral PFP cases was associated with GBS. He reported that FN had increased gadolinium uptake in the canalicular segment, labyrinth segment, and/or geniculate ganglion on MRI of the patients. In addition, the patient who had abducens paralysis with unilateral PFP had significant contrast enhancement in the caudal of the pons, FN mastoid segment, and abducens nerve on MRI. However, in a series of eight cases by Lima et al. (12), MRI was performed in five of the cases, and it was reported that contrast enhancement increased in FN only in one of them. Komori et al. (26) selected five regions along the intratemporal facial canal as the measurement sites of the facial nerve diameters: (1) the meatal foramen, (2) the cochleariform process, (3) the stapes, (4) the pyramidal eminence, and (5) the dike segment of the chorda tympani. Measurements as left and right were as follows, respectively (mm); meatal foramen (MF) 0.99±0.05 (0.87-1.11); 0.99±0.06 (0.89-1.15), Cochleariform process (CP) 1.39±0.10 (1.25-1.57); 1.39±0.09 (1.23-1.55), Stapes (S) 1.09±0.07 (0.95-1.23); 1.09±0.07 (0.93-1.21), Pyramidal eminence (PE) 1.62±0.07 (1.50-1.75); 1.61±0.07 (1.48-1.71), Emerging point of chorda tympani (EC) 2.14±0.24 (1.63-2.82) 2.15±0.16 (1.75-2.54). Although the same points were not used in our measurements, they are similar to each other. In our study, we measured the segment diameters of the facial nerve using temporal CT and MRI imaging.

In the consensus reports of Herman et al. regarding the use of corticosteroids in otology cases, they recommended the use of short-term corticosteroids in necessary cases according to the severity of the symptoms after the BP cases were well evaluated, and it was decided that they were definitely idiopathic (27). They recommended short-term corticosteroid therapy only in severe forms (Grades 5-6) and in patients without any of the signs and symptoms of Covid-19. They did not recommend routine nasopharyngeal swabs in patients presenting with PFP because PFP was not a definitive finding for Covid-19, and more importantly, the nasopharyngeal swab had limited reliability (40% false negativity). In other patients, only eye protection and follow-up were recommended. They published that BP patients with Covid-19 symptoms should be evaluated on a case-by-case basis by the responsible team after diagnostic tests. Oral antiviral therapy (valaciclovir 3g / day) was recommended only in shingles cases, as previously stated (27). The post-healing grade of all 42 patients who took steroids decreased to Grade 1. The post-healing grades of the patients not receiving steroids remained as Grade 1, one patient as Grade 2, and three patients as Grade 3. Although we understand that steroid therapy works partly, we see that spontaneous regression is more important. Current literature information regarding the Covid-19 period and our article is shown in Table 5 (12, 13, 16, 28, 29).

In a study on the incidence of Covid-19 and Bell's Palsy, it was reported that the incidence did not increase during the pandemic in the last five years. However, the fact that the PCR result of approximately 40% of the patients in this study is unknown may support both hypotheses in all the existing debates that the virus increases or reduces the true incidence of Bell's Palsy (30). Patients presenting with facial paralysis during the heaviest period of the pandemic may have been sent from the hospital without taking swab samples, which may obscure real interpretations.

CONCLUSION

Facial paralysis is a common phenomenon in ear, nose, and throat practice and requires priority treatment and follow-up. When we look at the two same time intervals before and after Covid from the data we have obtained from this study; We see that the frequency of facial paralysis has increased in the post-covid period. It has been emphasized in some studies that Covid-19 is a neurotropic virus. Since the Covid-19 virus is a new entity in the world, we think that it has an affinity for the facial nerve, although our knowledge about this virus is limited. For this reason, clinical follow-up of the facial nerve is important in Covid patients. Although there was no change in the approach to treatment, the patients were given routine Covid treatment. In addition, in accordance with the literature, we did not observe a significant difference in terms of improvement between patients who took steroids and those who did not.

Limitations of the study

In addition, patients were not given corticosteroids treatment for facial paralysis because the effects of corticosteroids were not known at the beginning of the pandemic. In Turkey, the official announcement date of the first patient was 10.03.2020, and we think that that group of patients who did not take a swab in the next three months presents as a neurotrophic symptom of the virus. Unfortunately, swab samples were not sent from those patients who did not have typical respiratory system findings.

Ethics Committee Approval: This study was approved by Adana City Training and Research Hospital Clinical Research Ethics Committee (Date:08.07.2021, No: 984).

Informed Consent: Written informed consent was obtained.

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RESEARCH ARTICLE
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Experiences with Head and Neck Pilomatrixoma

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ABSTRACT

Objective: The study aims to provide more information about the clinical features, diagnosis, and treatment of pilomatrixoma, of which little is known.
Materials and Method: The research retrospectively studies pilomatrixoma cases that were operated by a department of otorhinolaryngology between January 2018-October 2021.
Results: Pilomatrixoma is a benign tumor originating from the hair follicle matrix and is observed more frequently in women than in men. It is most commonly seen as a nodule in the head and neck region under the skin. This study examines 7 cases diagnosed as pilomatrixoma.
Discussion: Pilomatrixoma should also be especially considered in palpable superficial or ulcerated lesions in the preauricular region, and differential diagnosis of pilomatrixoma should be made with parotid tumors.

Keywords: Pilomatrixoma, head and neck, benign tumor

INTRODUCTION

Pilomatrixoma is a benign soft tissue tumor originating from the hair follicle matrix. Although Malherbe and Chenantais suggested in 1880 that this benign tumor originates from the sebaceous glands, Forbis and Hellwigshowed showed that this benign tumor arises from the cortex of the hair follicle and named it pilomatrixoma in 1961 (1).

Pilomatrixoma is more common in women than men and usually occurs in the first two years of life. It is most commonly seen as a single nodule under the skin in the head and neck region. However, cases have been found with multiple nodules (2-3).

The treatment for pilomatrixoma is surgical excision. Recurrence is rare, and if it does happen, a malignant pilomatrixoma variant should be suspected (3).

Pilomatrixoma is a rare tumor that is usually seen in the head and neck region and can be confused with malignancy. This study presents head and neck pilomatrixoma cases that have been operated upon and aims to increase awareness of its pathology.

MATERIALS AND METHOD

This article retrospectively studies pilomatrixoma cases that were operated upon by a department of otorhinolaryngology between January 2018-October 2021 and examines the patients' ages, complaints at presentation, location of the lesion, and dimensions, as well as preoperative and postoperative biopsy results. The patients' follow-ups were also recorded. Those who did not follow up were called and invited for a checkup.

RESULTS

The study includes seven patients whose pathology resulted in a pilomatrixoma diagnosis. Six of these patients were women. The age of the patients ranged from 10-64 years (M = 34.8). All of the patients presented with a slow growing mass.

The findings from the patients' physical examinations showed a well-circumscribed mass lesion on palpation. Four of the lesions were located in the parotid region (Figure 1), two were on the sternocleidomastoid muscle, and one was in the frontal region.

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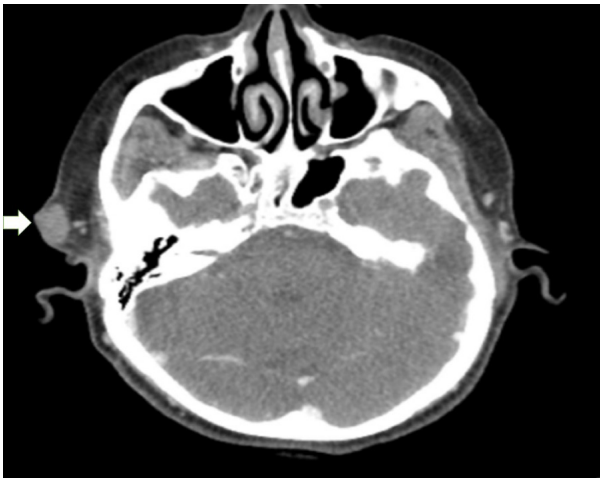

Figure 1: CT image of a 17x12mm contrast-enhancing solid mass lesion (White arrow) in the skin-subcutaneous fatty tissue at the right preauricular level.

All patients had a preoperative radiological examination. More than one imaging method was performed on some of the seven patients. Ultrasonography (USG) was used most frequently due to being non-invasive and easy to apply. However, USG cannot show the relationship of the mass with the parotid as well as computed tomography (CT) and magnetic resonance imaging (MRI) can, and USG may be insufficient regarding masses with a suspected malignant tumor. Therefore, MR and CT were requested for preoperative planning to better understand the relationship of the mass with the parotid gland. USG was run for 5 patients, CT for 3 patients (Figure 1), and an MRI for 1 patient were available. The radiological size of the masses ranged from 1 cm to 3 cm (*M* = 2.1 cm).

When deciding on which biopsy to perform, fine-needle aspiration biopsy (FNAB) was the most common choice due to its ease of application. However, incisional biopsy and Tru-cut biopsy were used in cases where FNAB was insufficient

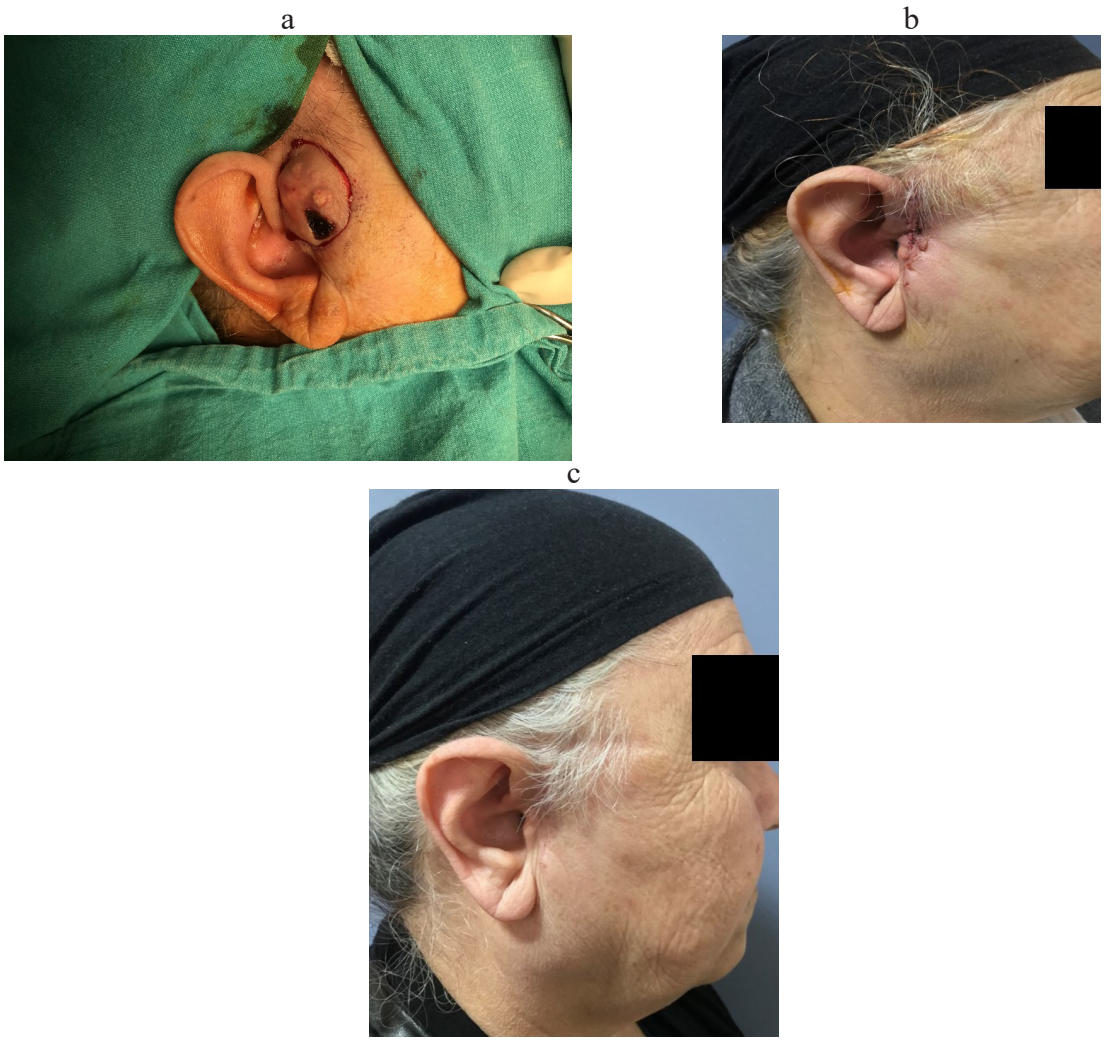

Figure 2: The mass lesion located in the right parotid lodge was excised by taking 2-3 mm from the intact tissue, with primary suturing used to close the defect that had formed. (a) Intraoperative, (b) postoperative 1st-day and (c) postoperative 10th-day images of the patient.

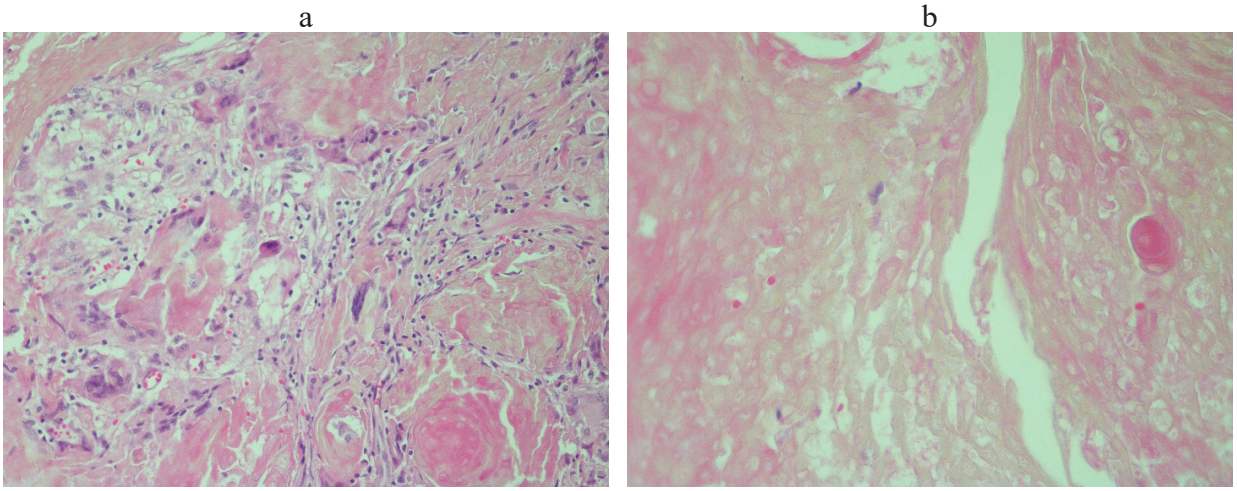

Figure 3: (a) Histopathological image of pilomatrixoma, ghost, and basophilic cells are shown at x20 magnification. (b) Histopathological image of ghost cell shown at x40 magnification.

or the tumor was clinically suspected of malignancy. FNAB was performed in two patients, Tru-cut biopsy was performed on one patient, and incisional biopsy was performed on one patient for diagnostic purposes. In two patients who underwent FNAB, the mass was located in the parotid. One patientis FNAB result was reported as keratinized cells and macrophages, while the other patient's was reported as perhaps compatible with mucoepidermoid carcinoma. The result from the patient who underwent Tru-cut biopsy was reported as benign neoplasia, and the result from the patient who underwent incisional biopsy was reported as pilomatrixoma.

Surgical treatment was applied to all seven patients, and the masses were excised with intact surgical margins and closed with primary suturing (Figure 2). The patient whose FNAB result was compatible with mucoepidermoid carcinoma was presented with a pathology report, and an additional neck dissection was performed. The final pathology reports for all patients were reported as pilomatrixoma. The pathological sizes of the specimens removed during surgery ranged from 0.4 cm to 3 cm (*M* = 1.9 cm).

The histopathological structure of pilomatrixoma involves irregular epithelial cell groups with ghost cells in the center and varying amounts of basophilic cells (Figure 3). The ghost cell is an enlarged eosinophilic epithelial cell with only cytoplasm that has lost its nucleus (4). The number of ghost cells gradually increases with time until the characteristic calcification and osteogenesis of pilomatrixoma occurs (5).

DISCUSSION

Pilomatrixoma is a generally hard and slow-growing benign tumor that develops from the hair follicle matrix and is covered with normal skin tissue. Its etiology is not fully known. This benign tumor has been reported to possibly occur as a result of a disruption in the cycle of the hair follicles (6). As a result of histochemical studies and electron microscopy studies, the belief has formed that these lesions originate from the basal cells of the epidermis. These primitive basal cells transform into hair matrix cells through an uncontrolled proliferation (7).

Although pilomatrixoma usually occurs as a single nodule, it can also occur as multiple nodules (8). Patients' having multiple nodules has been reported to possibly be associated with a familial predisposition to beta catenin gene mutations and to disorders such as myotonic dystrophy, Rubinstein-Taybi syndrome, Turner syndrome, Gardner syndrome, xeroderma pigmentosum, and basal cell nevus syndrome (9-10).In the case series studied in this article, a single nodule was present in all cases. The patients' histories and familial histories revealed no familial predisposition. In most cases, the skin over the tumor may become thinner or even covered with normal skin. In some cases, discoloration of the skin may occur due to ulceration. Patients usually do not have pain complaints. Pilomatrixoma can be located anywhere except the palms and soles of the feet and is especially common in the head and neck region (7, 11). All patients in the current study presented with a palpable mass and no additional symptoms, with one patient also having ulceration of the skin (Figure 2).

The characteristic calcifications of pilomatrixoma can be seen on plain radiographs, but diagnosis is difficult this way (12). USG is the most common imaging method used to aid in diagnosis. It is non-invasive, fast, and easy to apply. USG is important in terms of showing the depth of the lesion, its relationship with neighboring tissues, and calcifications (13). USG has been proposed as an alternative to CT and MRI for imaging preauricular masses in young children, as it can usually be performed without sedation or general anesthesia (12). However, CT and MRI are more helpful in determining the relationship of the preauricular lesion with adjacent structures, especially the parotid gland. Therefore, they provide more benefits in differentiating pilomatrixomas from primary parotid tumors and in preoperative planning. Pilomatrixoma usually appears as a non-contrast-enhancing, well-demarcated, subcutaneous lesion on a CT, whereas on an MRI, it appears as a soft tissue mass with homogeneous moderate signal intensity

on T1-weighted images and as a heterogeneous moderate-to-high signal intensity on T2-weighted images (12-13).

The diagnosis of this benign tumor can be confirmed by histopathological examination. FNAB is useful in the diagnosis of many tumors, as well as in the diagnosis of pilomatrixoma. However, pilomatrixoma aspirates also have properties similar to those in malignant tumors. Therefore, pilomatrixoma can be confused with tumors such as poorly differentiated basaloid cell carcinoma, keratinized squamous cell carcinoma, small cell carcinoma, and Merkel cell carcinoma. The nuclear morphology of pilomatrixoma helps to distinguish it from other tumors (14). The FNAB result of one patient in this study's case series was reported as compatible with mucoepidermoid carcinoma. Therefore, pilomatrixoma should be kept in mind even if a malignant tumor is reported when FNAB is performed due to a mass in the preauricular region.

The treatment for pilomatrixoma is surgery (3). After complete excision of the tumor, recurrence is rare, with malignancy rarely being reported (15). All patients in the current study were treated with surgical excision and cured. No recurrence was observed within at least a 1-year follow-up.

Pilomatrixoma should also be especially considered in palpable superficial or ulcerated lesions in the preauricular region, and a differential diagnosis should be made for it with parotid tumors. As was the case in this study's report, pilomatrixoma and malignancy can be confused pathologically with regard to fine needle aspiration biopsy. In such superficial or ulcerated lesions, a definitive diagnosis can be made with a Tru-cut biopsy or incisional biopsy. In this way, an unnecessary and extensive surgery can be avoided. However, if the lesion is a malignant tumor, care should be taken, as incisional biopsy will affect postoperative survival.

Ethics Committee Approval: This study was approved by Erciyes University Clinical Research Ethics Committee (Date: 14.09.2022, No: 2022/615).

Informed Consent: Written informed consent was obtained.

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RESEARCH ARTICLE
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Mean Platelet Volume and Red Blood Cell Distribution Width as Predictors of Post-Tonsillectomy Hemorrhage

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ABSTRACT

Objective: Post-tonsillectomy hemorrhage (PTH) is one of the most common sources of postoperative morbidity especially in children. Gender, age, tonsillectomy indication, surgical technique, surgeon's skill level, INR (International Normalized Ratio) and aPTT (activated Partial Thromboplastin Time) values, localized and systemic conditions have been described as risk factors for PTH. This study focuses on determining the effect mean platelet volume (MPV) and red blood cell distribution width (RDW) levels have on PTH.
Material and Methods: A retrospective, case-control study was conducted involving 40 patients with PTH and 40 patients without PTH. The patients who had diseases that might affect the levels of MPV or RDW, were excluded. Median MPV and RDW values were compared for the two groups.
Results: The MPV median value was 7.73±0.93 fL in the hemorrhage group and 8.38±1.27 fL in the control group (p=0.038). The RDW median value was 15.4%±1.61 in the hemorrhage group and 14.6%±1.21 in the control group (p=0.007). It was determined that high RDW levels increased PTH and high MPV levels decreased PTH.
Conclusion: Low MPV value and high RDW values can be useful in predicting the risk of PTH. However, more research is needed to better understand the association between RDW values, MPV values, and PTH.
Keywords: Post-tonsillectomy hemorrhage, tonsillectomy, postoperative complications, RDW, MPV

INTRODUCTION

Otolaryngologists conduct tonsillectomy as one of the most common surgical procedures (1). Obstructive sleep apnea and recurrent tonsil infections are the most prevalent indications for tonsillectomy. Velopharyngeal insufficiency, hemorrhage, dehydration, post-obstructive pulmonary edema, and nasopharyngeal stenosis are among the post-operative complications after tonsillectomy (2). With a reported prevalence of 1–5%, post-tonsillectomy hemorrhage (PTH) is a serious complication that causes postoperative morbidity (3). PTH remains a fatal complication despite all attempts to decrease it, including innovations in surgical methods and additional instruments and materials for effective hemostasis. Gender, age, tonsillectomy reason, surgical method, surgeon's competence level, and INR and aPTT levels are all reported risk factors for PTH (4–9).

Several recent research studies have looked at the relationship between hemorrhage and numerous blood. Red blood cell distribution width (RDW) and mean platelet volume (MPV) are the two that stand out the most among these parameters (10–13). Coagulation requires platelets, which are composed of megakaryocytes in the form of a disc. The importance of

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the MPV level in determining platelet activity may be shown in enzymatic and metabolic processes, where it was shown that bigger platelets were more effective than their smaller counterparts. This finding suggests that larger platelets have a greater impact on platelet activity. Evidence suggesting an increased MPV value results in a shortened bleeding period is conclusive (10).

When analyzing the erythrocyte population, the RDW value is what is used to determine variability (14). RDW is frequently present in the majority of diseases wherein reticulocytes are released into circulation prior to maturation. Increased RDW values have been a common denominator in cardiovascular disease instances, intestinal inflammation, heart failure cases, and cases of celiac disease not to mention being the differential diagnosis for anemia (15). In addition, an increase in RDW has been linked to increases in inflammatory markers (16,17).

To the best of our knowledge, the association between the RDW value and PTH as well as a link between MPV value and PTH has not been investigated thus far. In this study, our aim is to analyze the relationship between PTH, RDW, and MPV values.

MATERIAL AND METHODS

The records of participants who had a tonsillectomy in the Otolaryngology Department of a Tertiary Training and Research Hospital between January 1, 2008, and December 31, 2016 were analyzed for this retrospective, case-controlled research. All of the procedures that were utilized in the research that included human subjects were carried out in a manner that was compliant with the ethical standards that were established by the institution and/or the national research committee. In addition, all of the procedures were carried out in accordance with the original Helsinki statement of 1964 and any subsequent revisions or other ethical standards that were comparable The hospital's ethical committee accepted the trial (number: B.10.1.TKH.4.34.H.GP.0.01/120). Each participant in the research gave their own written informed consent, and this consent was collected individually.

A total of 1519 patient charts were analyzed. 9 of the patients were not included in the study due to lack of the blood test results and 155 of the patients due to having a disease effecting RDW and MPV values, thus, there were a total of 1355 participants in the research. 1315 patients had no PTH complication. 40 patients who had PTH were defined as the Hemorrhage Group, and the median RDW and MPV values were calculated for this group.

The upper limit of normal (ULN) and lower limit of normal (LLN) of RDW and MPV data collected from 1315 patients was calculated with the mean±2 standard deviations (SD): this range of values was regarded as normal. Forty patients of similar age and sex to the Hemorrhage Group, whose rdw and mpv values are within the normal range were defined, were randomly selected as the Control Group.

The surgeries were performed by several otolaryngology specialists, using cold dissection. Operations were performed under general anesthesia in the Rose position with orotracheal intubation. Boyle–Davis gag was used to expose the tonsils. Hemostasis was achieved using bipolar electrocoagulation.

Statistical analysis

The SPSS Version 2.0 application (IBM Corporation; Armonk, NY, USA) was used to conduct the statistical analysis. A descriptive statistical analysis was carried out (mean, median, and standard deviation). The Independent Sample T Test was performed to compare the two groups for normal distribution of quantitative variables. The ULN and LLN of RDW and MPV values were computed using the mean 2±SD values within this range were regarded normal, and the mean 2±SD of logarithmic converted data values outside this range were considered abnormal.

RESULTS

The study comprised 40 hemorrhage and 40 control cases in total. The Hemorrhage Group had 26 patients, 65 percent of whom were male; similarly, the Control Group included 26 patients, 65 percent of whom were male. The Hemorrhage Group had a median age of 21.6±15.95 years, whereas the Control Group had a median age of 21.5±14.93 years. No statistically significant difference existed between the groups (p=0.897). Table 1 shows the demographic characteristics of the patients.

Analysis of total blood count factors discovered MPV values to be 7.73±0.93 fL in the Hemorrhage Group and 8.38±1.27 fL in the Control Group. The difference between the groups was statistically significant (p=0.038). Similarly, RDW median value was 15.4%±1.61 in the Hemorrhage Group and 14.6%±1.21 in the Control Group. A statistically significant difference between the groups was also found (p=0.007) (Table 2).

Table 1: Demographic data of study population

		Gender	Age (median value)	
Hemorrhage group	Male	26(65%)	21.6±15.95	p=0.897
	Female	14(35%)		
Control group	Male	26(65%)	21.5±14.93	
	Female	14(35%)		

p< 0.05

Table 2: Comparison of MPV and RDW between hemorrhage group and control group

	Hemorrhage group (median value)	Control group (median value)	
MPV	7.73±0.93 fL	8.38±1.27 fL	p=0.038
RDW	15.4%±1.61	14.6%±1.21	p=0.007

MPV: Mean platelet volume, RDW: Red cell distribution width

DISCUSSION

This study concluded that value of MPV in patients with PTH was lower than in patients without PTH, however, the value of RDW in patients with PTH was more elevated. Therefore, we think that MPV and RDW levels may be used as indicators for PTH. Thus, a shorter bleeding time is a consequence of an increased MPV value.

MPV is a very important marker used to clarify the platelets activity and function of the platelets. Platelets with a larger volume include a greater number of prothrombotic components, including beta-thromboglobulin, thromboxane A2, and adhesion molecules. Thus, a shorter bleeding time is a consequence of an increased MPV value (10,18). The literature forwarded evidence of an association between elevated MPV values and cerebrovascular diseases, congestive heart failure, myocardial infarction and hypertension (19–21). Increased MPV levels are linked to a greater risk of mortality from ischemic heart disease, according to Slavka et al., with hazard ratios equivalent to smoking or obesity (22). On the other hand, reduced MPV levels are linked to a longer bleeding period and a higher risk of bleeding (10,18). In the same vein, the current study indicated that the levels of MPV in the PTH group were significantly lower than those in the control group.

RDW details the percentage change in the size and volume of a red blood cell in the peripheral blood. Higher RDW values suggest more variance in red blood cell size and volume. Several studies have found a link between RDW levels and vascular events. RDW values were greater in individuals with stable coronary artery disease compared to those with normal coronary angiography, according to a research by Çetin et al (23). Patients with higher RDW values were shown to have a greater likelihood of suffering from coronary artery disease and carotid plaque in a study conducted by Wen and colleagues (24). According to some experts, a high value of RDW might be a sign of persistent inflammation, which could lead to vascular events (16,17). Additionally, inflammation may have an effect on the process of erythropoiesis as well as the half-life of erythrocytes in circulation, leading to an increase in RDW levels. (25). According to the findings of Karabulut and colleagues, adult patients with epistaxis had a greater RDW value than the general population (10). In our study, we reported that the RDW value was significantly higher in the Hemorrhage Group than in the Control Group. Chronic inflammation could increase erythropoiesis which might explain the presence of high RDW in these patients.

The present research has two flaws: first, it is a retrospective study conducted at a single center; second, the data used in the study was taken from patient files. As a result, the results need to be corroborated in prospective studies conducted at many centers.

CONCLUSION

In conclusion, low value of MPV and high value of RDW can be useful in predicting the risk of post-tonsillectomy hemorrhage. Further study is needed, however, to better understand the link between RDW, MPV, and post-tonsillectomy bleeding.

Ethics Committee Approval: This study was approved by University of Health Sciences, Umraniye Training and Research Hospital Clinical Research Ethics Committee (Date:17.10.2018, No: B.10.1.TKH.4.34.H.GP.0.01/120).

Informed Consent: Written informed consent was obtained.

Peer Review: Externally peer-reviewed.

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

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CASE REPORT
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Ear Reconstruction with Preauricular Transposition and Helical Chondrocutaneous Advancement Flap After Excision of Trichilemmal Carcinoma

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ABSTRACT

Trichilemmal carcinoma (TLC) is a fairly uncommon cutaneous malignancy with a favorable prognosis in the majority of cases. The gold standard of treatment is extensive local excision. The purpose of this study is to demonstrate the outcomes of a single-stage surgical approach that preserves the ear's anatomical characteristics. We present a case of a 70-year-old man who was treated with a single-stage surgical technique for trichilemmal cancer of the ear. After six months, the ear seemed to have entirely healed with no evidence of recurrence.
Keywords: Trichilemmal carcinoma, single-stage surgical approach, helical chondrocutaneous advancement flap, preauricular transposition flap, ear reconstruction

INTRODUCTION

Trichilemmal carcinoma (TLC) is a relatively uncommon cutaneous adnexal tumor that most usually appears on the sun-exposed skin of the elderly face (1). It appears clinically as an asymptomatic nodular or polypoid tumor with ulceration and squamas similar to basal cell carcinoma, squamous cell carcinoma, or keratoacanthoma (2). We describe a case of a 70-year-old man with auricular trichilemmal cancer.

CASE PRESENTATION

In June 2020, a 70-year-old man presented to our hospital with a nodular, painless lesion measuring 3 * 2.5cm developing from the triangular fossa of the auricle (Figure 1). A biopsy that was performed a year before in another institution classified it as squamous cell carcinoma. A second biopsy was performed, and the pathology findings confirmed the presence of a TLC. No other abnormalities were seen on magnetic resonance imaging of the head and neck. We selected a single-stage approach to achieve a complete excision of the tumor with a satisfactory aesthetic and functional result. The surgery was performed under general anesthesia. The lesion was excised through a wide local excision (Figure 2). To address the resulting tissue defect, a helical chondrocutaneous advancement flap and a preauricular transposition flap were employed (Figure 3). Six months after the surgery, the ear seemed to be completely healed, with no recurrent symptoms (Figure 4).

DISCUSSION

Headington was the first to coin the term "TLC" (3). The majority of patients with TLC are men aged 60-80 years and women over 80 years old. This difference in age distribution is likely due to the fact that women generally pay more attention to sun protection (4). The pathophysiology is unknown; however, sun exposure seems to be the primary causing factor. UV radiation, solid organ transplantation, immunosuppression, scarring, burns and hereditary illnesses such as xeroderma pigmentosum and Cowden disease are all established as risk factors for this malignancy (5). Given the recent progressive increase in the incidence of TLC, one should be alert to the

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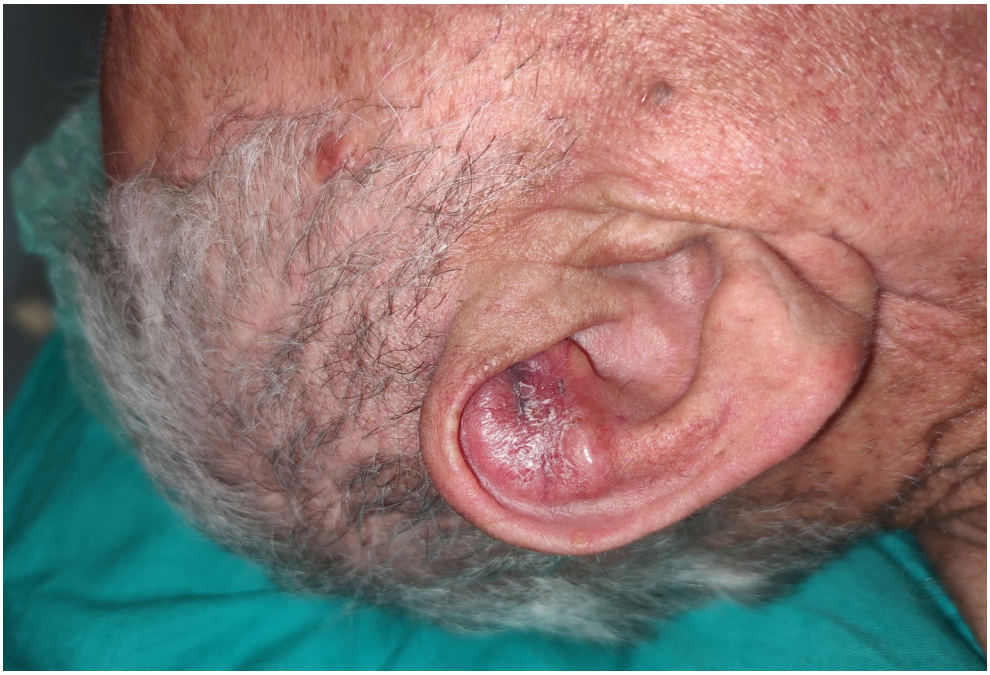

Figure 1: Tumor arising from triangular fossa of auricle.

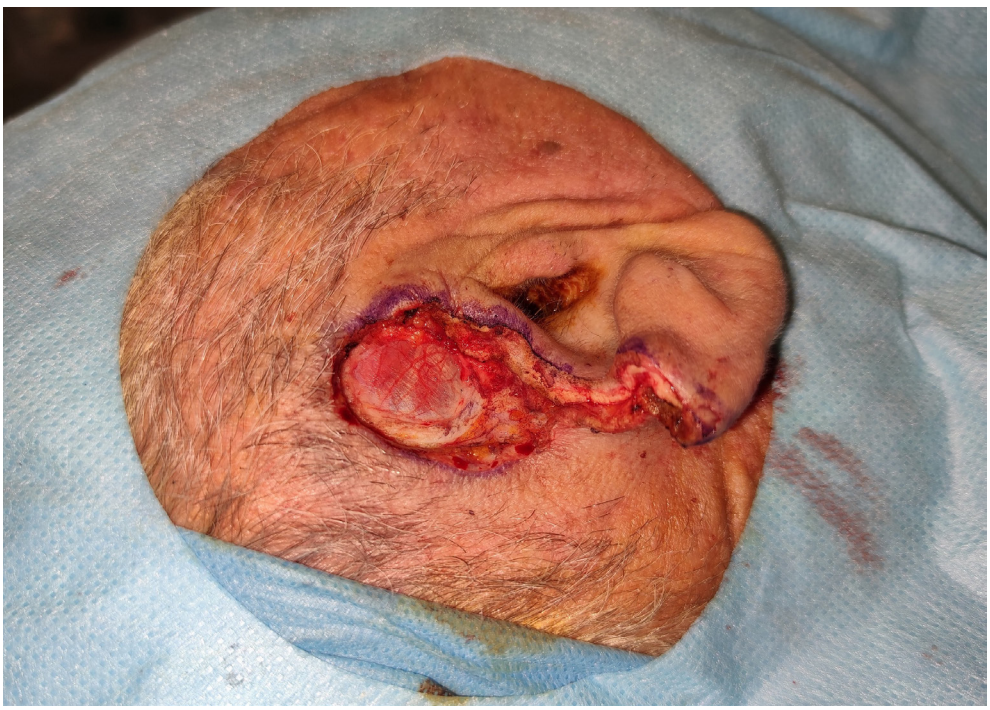

Figure 2: Wide local excision of lesion

possibility of TLC when faced with adnexal skin tumors of the head and neck (4).

Currently, the differential diagnosis of TLC is mainly based on Hematoxylin-eosin (HE) staining. Periodic acid–Schiff (PAS) staining has also been widely used. However, we cannot rely on PAS staining alone to diagnose TLC (6,7). For cases in which differential diagnosis is difficult, special stains may be helpful.

Differential diagnosis of TLC from cancers such as clear-cell squamous cell carcinoma, clear-cell basal cell carcinoma, balloon cell melanoma, hidradenocarcinoma, sebaceous carcinoma, and metastatic clear-cell adenocarcinoma can be made with special stains (4). While TLC stains positively with Pan CK, CK15, Ki-67, p63, p53, and CK1, it stains negatively with S-100, CEA, HMB-45, Vimentin, MelanA, and SMA (4).

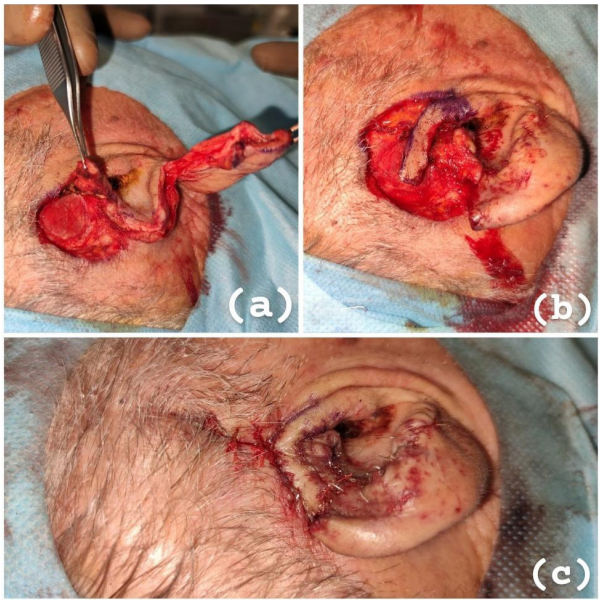

Figure 3: (a) Helical chondrocutaneous advancement flap harvested (b) preauricular transposition flap harvested (c) intraoperative appearance after reconstruction.

TLC has a slow-growing clinical history and is susceptible to curative resection with standard surgery (5). However, incidences of profound invasion and local recurrence have been recorded occasionally in the literature. Furthermore, in immunocompromised transplant recipients, TLC may metastasize to the liver and lung, with a poor prognosis (8).

The first line treatment for curative purpose is surgical excision with 1 cm safety margins and no adjuvant therapy. Postoperative monitoring of the patient is required to allow for early detection of recurrence and metastases (9). Mohs micrographic surgery is an effective treatment method for malignant trichilemmal tumors (2). We were able to do an intervention that preserved the anatomy of the ear in terms of size, shape and helix fold without jeopardizing the procedure's safety in terms of total tumor removal. Using two flaps, we restored the helix profile and original anatomical thickness. Finally, under general anesthesia, this single-staged method may be conducted in the same day clinic.

CONCLUSION

Our single-stage surgical approach preserved the ear's anatomy after full removal of the tumor.

Informed Consent: Written informed consent was obtained.

Peer Review: Externally peer-reviewed.

Conflict of Interest: The author has no conflict of interest to declare.

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

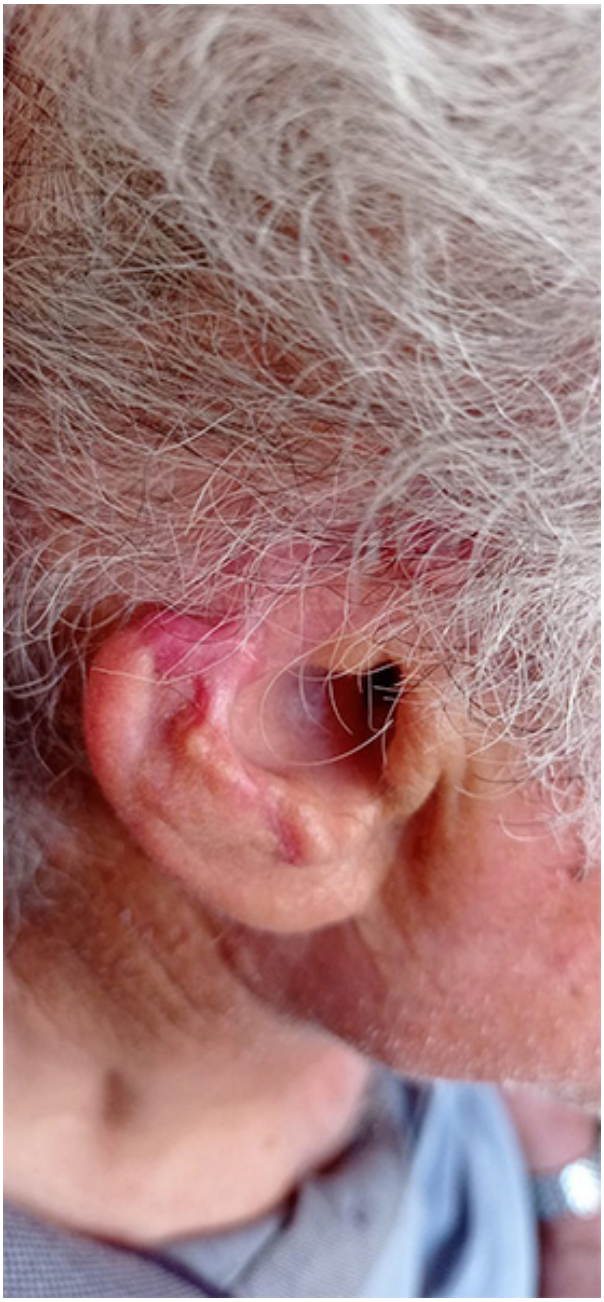

Figure 4: Six months after the operation, the ear appeared completely healed, with no signs of recurrence.

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- The independence of research must be clear; and any conflict of interest or must be disclosed.
- In experimental studies with human subjects, written informed consent of the participants who decide to participate in the research must be obtained. In the case of children and those under wardship or with confirmed insanity, legal custodian's assent must be obtained.
- If the study is to be carried out in any institution or organization, approval must be obtained from this institution or organization.
- In studies with human subject, it must be noted in the method's section of the manuscript that the informed consent of the participants and ethics committee approval from the institution where the study has been conducted have been obtained.

Ethics Committee Approval and Informed Consent

The Turkish Journal of Ear Nose and Throat (Tr-ENT) takes as principle to comply with the ethical standards of World Medical Association (WMA) Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects revised in 2003 and WMA Statement on Animal Use in Biomedical Research revised in 2016.

An approval of research protocols by the Ethics Committee in accordance with international standards mentioned above is required for experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. For manuscripts concerning experimental research on humans, a statement should be included that shows that written informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. Information on patient consent, the name of the ethics committee, and the ethics committee approval number should also be stated in the Materials and Methods section of the manuscript. It is the authors' responsibility to carefully protect the patients' anonymity. For photographs that may reveal the identity of the patients, signed releases of the patient or of their legal representative should be enclosed.

Author's Responsibilities

It is authors' responsibility to ensure that the article is in accordance with scientific and ethical standards and rules. And authors must ensure that submitted work is original. They must certify that the manuscript has not previously been published elsewhere or is not currently being considered for publication elsewhere, in any language. Applicable copyright laws and conventions must be followed. Copyright material (e.g. tables, figures or extensive quotations) must be reproduced only with appropriate permission and acknowledgement. Any work or words of other authors, contributors, or sources must be appropriately credited and referenced.

All the authors of a submitted manuscript must have direct scientific and academic contribution to the manuscript. The author(s) of the original research articles is defined as a person who is significantly involved in "conceptualization and design of the study", "collecting the data", "analyzing the data", "writing the manuscript", "reviewing the manuscript with a critical perspective" and "planning/conducting the study of the manuscript and/or revising it". Fund raising, data collection or supervision of the research group are not sufficient roles to be accepted as an author. The author(s) must meet all these criteria described above. The order of names in the author list of an article must be a co-decision and it must be indicated in the Copyright Agreement Form. The individuals who do not meet the authorship criteria but contributed to the study must take place in the acknowledgement section. Individuals providing technical support, assisting writing, providing a general support, providing material or financial support are examples to be indicated in acknowledgement section.

All authors must disclose all issues concerning financial relationship, conflict of interest, and competing interest that may potentially influence the results of the research or scientific judgment.

When an author discovers a significant error or inaccuracy in his/her own published paper, it is the author's obligation to promptly cooperate with the Editor to provide retractions or corrections of mistakes.

Responsibility for the Editor and Reviewers

Editor-in-Chief evaluates manuscripts for their scientific content without regard to ethnic origin, gender, sexual orientation, citizenship, religious belief or political philosophy of the authors. He/She provides a fair double-blind peer review of the submitted articles for publication and ensures that all the information related to submitted manuscripts is kept as confidential before publishing.

Editor-in-Chief is responsible for the contents and overall quality of the publication. He/She must publish errata pages or make corrections when needed.

Editor-in-Chief does not allow any conflicts of interest between the authors, editors and reviewers. Only he has the full authority to assign a reviewer and is responsible for final decision for publication of the manuscripts in the Journal.

Reviewers must have no conflict of interest with respect to the research, the authors and/or the research funders. Their judgments must be objective.

Reviewers must ensure that all the information related to submitted manuscripts is kept as confidential and must report to the editor if they are aware of copyright infringement and plagiarism on the author's side.

A reviewer who feels unqualified to review the topic of a manuscript or knows that its prompt review will be impossible should notify the editor and excuse himself from the review process.

The editor informs the reviewers that the manuscripts are confidential information and that this is a privileged interaction. The reviewers and editorial board cannot discuss the manuscripts with other persons. The anonymity of the referees must be ensured. In particular situations, the editor may share the review of one reviewer with other reviewers to clarify a particular point.

PEER REVIEW

Peer Review Policies
Only those manuscripts approved by its every individual author and that were not published before in or sent to another journal, are accepted for evaluation.

Submitted manuscripts that pass preliminary control are scanned for plagiarism using iThenticate software. After plagiarism check, the eligible ones are evaluated by editor-in-chief for their originality, methodology, the importance of the subject covered and compliance with the journal scope.

The editor hands over the papers matching the formal rules to at least two national/international referees for double-blind peer review evaluation and gives green light for publication upon modification by the authors in accordance with the referees' claims.

Responsibility for the Editor and Reviewers
Editor-in-Chief evaluates manuscripts for their scientific content without regard to ethnic origin, gender, citizenship, religious belief or political philosophy of the authors. Editor-in-Chief provides a fair double-blind peer review of the submitted articles for publication and ensures that all the information related to submitted manuscripts is kept as confidential before publishing.

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Editor-in-Chief evaluates manuscripts for their scientific content without regard to ethnic origin, gender, citizenship, religious belief or political philosophy of the authors and ensures a fair double-blind peer review of the selected manuscripts. The selected manuscripts are sent to at least two national/international referees for evaluation and publication decision is given by Editor-in-Chief upon modification by the authors in accordance with the referees' claims. Editor-in-Chief does not allow any conflicts of interest between the authors, editors and reviewers and is responsible for final decision for publication of the manuscripts in the Journal. Reviewers' judgments must be objective. Reviewers' comments on the following aspects are expected while conducting the review.

- Does the manuscript contain new and significant information?
- Does the abstract clearly and accurately describe the content of the manuscript?
- Is the problem significant and concisely stated?
- Are the methods described comprehensively?
- Are the interpretations and consclusions justified by the results?
- Is adequate references made to other Works in the field?
- Is the language acceptable?

Reviewers must ensure that all the information related to submitted manuscripts is kept as confidential and must report to the editor if they are aware of copyright infringement and plagiarism on the author's side.

A reviewer who feels unqualified to review the topic of a manuscript or knows that its prompt review will be impossible should notify the editor and excuse himself from the review process.

The editor informs the reviewers that the manuscripts are confidential information and that this is a privileged interaction. The reviewers and editorial board cannot discuss the manuscripts with other persons. The anonymity of the referees is important.

Manuscript Organization and Submission

The manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2015 - http://www.icmje.org/icmje-recommendations.pdf). Author(s) are required to prepare manuscripts in accordance with the CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behavior.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at https://dergipark.org.tr/tr/journal/3565/submission/step/manuscript/new Manuscripts submitted via any other medium will not be evaluated.

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

Author(s) are required to submit the following documents together with the manuscript and must ensure that the abstract and keywords are in line with the standards explained in below.

- **Copyright Agreement Form**
- **Author Form and ICMJE Potential Conflict of Interest Disclosure Form**
- **Ethics Committee Approval**
- **Cover Letter to the Editor**
- **Title Page**: A separate title page should be submitted with all submissions and this page should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, academic degree(s) and ORCID ID(s) of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfil the authorship criteria.

Abstract: Abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, Materials and Methods, Results, and Conclusion). Abstracts of Case Reports and Reviews should be unstructured. Abstracts should be 200-250 words.

Keywords: Each submission must be accompanied by a minimum of 3 to a maximum of 6 keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (http://www.nlm.nih.gov/mesh/MBrowser.html) .

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, Material and Method, Results, Discussion, and Conclusion subheadings..

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.

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

Invited Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

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

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, 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.

Tables

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

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

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

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

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

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

Revisions

When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over. Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within two days of their receipt of the proof. The latest status of the submitted manuscripts and other information about the journal can be accessed at http://tr-ent.com. The editorial and publication processes of the journal are conducted in accordance with the guidelines of the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice). An ORCID ID is required for all authors during the submission of the manuscript. The ID is available at http://orcid.org with free of charge.

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Periodicals: Author(s) Last Name initial(s) name of author(s) (if there are six or fewer authors, all authors should be written; if the number of authors are seven or more, only the first six of the authors should be written and the rest as "et al"). The title of the article, the abbreviated name of the journal according to the Index Medicus, Year; Volume (Issue): The first and last page numbers.

Example: Robson A, Greene J, Ansari N, Kim B. Eccrine porocarcinoma (malignant eccrine poroma): a clinicopathologic study of 69 cases. The American Journal of Surgical Pathology 2001;25:710-20. Books: Surname of the author(s) initial name(s) of author(s). The name of the book. The edition number. Place of publication: Publisher, Publication year.

Book chapters: The author (s) surname of the chapter initial (s) letter of the name. Section title. In: Surname of editor (s) initial (s) letter of first name (s) ed / eds. The name of the book. Edition number. Place of publication: Publisher, year of publication: The first and last page numbers of the chapter. Web address: If a "web" address is used as the reference address, the web address date should be given in brackets with the address. The DOI (Digital Object Identifier) number must be provided, when a web access article used in the text as a reference.

Example: AB Author, CD Author. Title of document. Retrieved from http://Web address (Accession date: aa/bb/2016).

Congress papers:

Thesis: Maden KL. Experimental investigation of the ..... Master Thesis, Health Science Institute of Ankara University, Ankara, 2005.

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  - Including disclosure of any commercial or financial involvement.
  - Confirming that the statistical design of the research article is reviewed.
  - Confirming that last control for fluent English was done.
  - Confirming that journal policies detailed in Information for Authors have been reviewed.
  - Confirming that the references cited in the text and listed in the references section are in line with NLM.
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- Acknowledgement of the study "in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration.
- Statement that informed consent was obtained after the procedure(s) had been fully explained. Indicating whether the institutional and national guide for the care and use of laboratory animals was followed as in "Guide for the Care and Use of Laboratory Animals".
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- Main Manuscript Document
  - The title of the manuscript
  - Abstract 200-250 words
  - Key words: 3 - 6 words
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