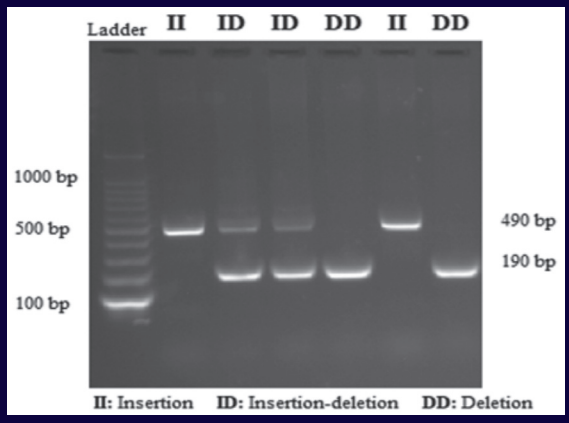
Indexed in PubMed and Web of Science

E-ISSN 2667-7474

Volume 62 ~ Issue 3 ~ September 2024

# Turkish Archives of Otorhinolaryngology

Official Journal of the
Turkish Otorhinolaryngology
Head and Neck Surgery Society




## Angiotensin-Converting Enzyme Insertion/Deletion Gene Polymorphism in Chronic Rhinosinusitis with Nasal Polyps

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### Original Investigations





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# Turkish Archives of Otorhinolaryngology
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**Web:** www.galenos.com.tr **Publisher Certificate Number:** 14521

**Publication Date:** September 2024
**E-ISSN:** 2667-7474

International scientific journal published quarterly.

Turkish Archives of Otorhinolaryngology
Türk Otorinolarengoloji Arşivi

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Turkish Archives of Otorhinolaryngology
Türk Otorinolarengoloji Arşivi

Contents

# Risk Factors of Post-Tonsillectomy Bleeding and Differences Between Children and Adults: Implications for Risk Assessment

Original Investigation

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## Abstract

**Objective:** To investigate the association between clinical factors and post-tonsillectomy hemorrhage (PTH) including rebleeding episodes.

**Methods:** The medical records of 1,082 patients who underwent tonsillectomy between May 2018 and April 2019 were reviewed. The entire study cohort included 431 (39.7%) children aged less than six years and 292 (26.9%) adults older than 15 years. Data on patient demographics, surgical indication, dissection technique, tonsils' grade, postoperative analgesia, surgeon's experience, the season of surgery, management of hemorrhage, length of hospital stay, and rebleeding episode were noted.

**Results:** Postoperative hemorrhage occurred in 87 cases (8.0%) including 32 children (4.0% of children) and 55 adults (18.8% of adults). Age, surgical indication, tonsils' grade, and postoperative use of non-steroidal anti-inflammatory drugs (NSAIDs) were risk factors found to be statistically significant for PTH in univariate analysis ($p<0.05$). Multivariable analyses identified patients older than 15 years and those who received postoperative NSAIDs to be risk factors of PTH [Odds ratio (OR): 15.5, 95% confidence interval (CI): 7.68-31.27, $p<0.001$, OR: 0.22, 95% CI: 0.11-0.44, $p<0.001$, respectively]. About one out of every 60 (1.5%) children had severe oropharyngeal bleeding, whereas every 12$^{th}$ (8.2%) patient of those aged >15 years had severe hemorrhages that warranted surgical hemostasis in the operating room ($p<0.001$).

**Conclusion:** The risk of bleeding after tonsillectomy was significantly higher in adults and users of NSAIDs postoperatively. Also, the evidence of minor bleeding increased the risk of a second bleeding episode in adulthood.

**Keywords:** Tonsillectomy, complications, postoperative hemorrhages, oral hemorrhage, risk factors, nonsteroidal anti-inflammatory agents.

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***Cite this article as:*** *Öcal B, Günay MM, Keseroğlu K, Mutlu M, Akyıldız İ, Saka C, Çadallı Tatar E, Korkmaz MH. Risk Factors of Post-Tonsillectomy Bleeding and Differences Between Children and Adults: Implications for Risk Assessment. Turk Arch Otorhinolaryngol. 2024; 62(3): 81-87*

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**Received Date:** 28-12-2023
**Accepted Date:** 07-06-2024

DOI: 10.4274/tao.2024.2023-10-2

## Introduction

Tonsillectomy is one of the most common surgical procedures performed in children worldwide and less common in adults. Postoperative hemorrhage remains the most significant complication of this surgery. Reported hemorrhage rates range from 0% to 20-30%, and this wide range has been attributed to several features

of patients (1,2). The most widely used classification that differentiates bleeding episodes as primary (occurring in the first 24 hours) and secondary (occurring after >24 hours), does not refer to the severity or frequency of bleeding (3). Some patients may present with a history of blood-tinged mucus with a normal oropharyngeal exam, while others may have active bleeding that warrants surgical intervention. Several studies have reported postoperative hemorrhage among their inclusion criteria, whereas some only included patients who needed surgical interventions, while others included patients even with negative examinations (4,5). There is no standardized approach especially to a non-active bleeding episode (including cases with normal oropharyngeal examination or blood clots in the tonsillar fossa without active bleeding) in which the management remains mostly institution-based (6-8). To develop a safe and accurate decision-making process, the risk of rebleeding should also be analyzed in patients being observed or undergoing surgical intervention.

This study primarily aimed to assess the association between clinical risk factors and post-tonsillectomy hemorrhage (PTH). Secondly, we attempted to describe the bleeding profiles and analyze the frequency of rebleeding episodes. Thus, we can define the characteristics of the patients who need surgical intervention or who can be managed by observation and conservative precautions.

## Methods

A retrospective review was done of the medical records of all patients undergoing tonsillectomy (with or without adenoidectomy) from May 1, 2018, to April 1, 2019. This study was reviewed and approved by the Institutional Review Board of Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital (approval no: 53/11, date: 06.08.2018). Informed consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data.

Our hospital is a tertiary care center where approximately 1000 tonsillectomies are performed annually in the pediatric otolaryngology department. Extracapsular tonsillectomy is done in all cases with cold steel, or bipolar cautery. Most patients are discharged the day after the surgical procedure. Standard pain medication regimens include paracetamol syrup (10-15 mg/kg/dose every 4-6 h) with or without ibuprofen syrup (5-10 mg/kg/dose every 6-8 h). We also suggest dexketoprofen effervescent tablet (25 mg three times) to adults as needed.

All patients presenting to the emergency department (ER) with PTH were referred to our department after the initial examination made by the ER physicians. Those patients were re-examined by ear, nose, and throat specialists in our department. Our clinical policy regarding PTH management is to admit almost all patients with a recent history of bleeding for an observation period of at least 24 hours, regardless of the absence of active bleeding. Oral intake was stopped for 24 hours. Intravenous access was maintained for fluid replacement and empiric antibiotic therapy. The history of hemorrhage varied among patients with PTH ranging from a blood-tinged mucus to severe arterial bleeding. Following our clinical policy, bleeding severity was stratified at the time of initial oropharyngeal examination as follows; grade 1: no bleeding or clot, grade 2: a clot in the tonsillectomy bed without active bleeding, grade 3: venous oozing, or grade 4: arterial bleeding (7). If the inspection revealed blood clots in the tonsillar fossa (grade 2), clots were removed to ensure that there is no ongoing bleeding underneath. If there was oozing or active bleeding (grade 3 or 4, respectively), a lidocaine %2 and epinephrine-soaked-gauze tampon were firmly applied to the tonsillar fossa. In cases of persistent hemorrhage, the patient was directed to the operating room (OR) to control the hemorrhage with bipolar diathermy and/or cautious ligature application under general anesthesia.

All patients, both children and adults, who presented to the ER with hemorrhage following tonsillectomy were included in the study. PTH was defined as any bleeding event after extubation. Patients were excluded if they did not have documented oropharyngeal examination. Also, patients with detected coagulopathy preoperatively, diagnosed, or suspected malignancy of the tonsils were excluded from the study.

Data on patient's demographic, infectious versus obstructive indication for tonsillectomy, dissection technique, the grade of tonsil size, postoperative analgesia, the experience of the surgeon, the season of surgery, management of hemorrhage, blood transfusion, length of hospital stay after an admission, rebleeding episodes were retrieved. Tonsil size was subjectively measured using a grading scale preoperatively. In grade 1, tonsils occupied less than 25% of the lateral dimension of the oropharynx, as measured between the medial borders of the anterior pillars. In grade 2, tonsils occupied 26% to 50% of the lateral dimension of the oropharynx. In grade 3, the tonsils occupied between 50% and 75% of the pharyngeal space. In grade 4, the tonsils occupied more than 75% of the pharyngeal space.

### Statistical Analysis

The database was built using the SPSS® software (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.), also the software used for data statistical analysis. Categorical variables are presented as frequencies and percentages, continuous variables as means and standard deviations, or as medians and interquartile amplitudes if variables were not normally distributed. Categorical variables were compared using Fisher's exact test or the chi-square test.

Continuous and categorical variables were compared by the Mann-Whitney U test. Univariate and multivariate logistic regression analyses were done to examine the potential predictors of the bleeding event. The odds ratio (OR) and 95% confidence intervals (CIs) were also calculated. All reported p-values are two-tailed with a p-value of 0.05 indicating statistical significance.

## Results

Of the 1,082 patients included, 607 (56.1%) were male and 475 (43.9%) were female; 431 (39.7%) patients were younger than 6 years, 359 (33.3%) aged between 7 to 15 years, and 292 (26.9%) were older than 15 years. Postoperative hemorrhage occurred in 87 cases (8.0%) including 32 children (4.0% of children) and 55 adults (18.8% of adults). The rates for primary and secondary bleeding were 1.4% and 6.6%, respectively. Primary bleeding occurred in 0.6% of the children and 3.4% of the adults, whereas secondary bleeding was observed in 3.4% of the children and 15.4% of the adults.

### Association of Variables with PTH

Age, indication for tonsillectomy, grade of tonsil size, and postoperative use of non-steroidal anti-inflammatory drugs (NSAIDs) were identified as the risk factors significantly related to PTH in univariate analysis. Patients aged >15 years had a higher incidence of PTH than those aged <15 years (18.8% vs 4.1%, p<0.001). Patients undergoing tonsillectomy for chronic recurrent tonsillitis had a higher risk than those who underwent the procedure for chronic upper airway obstructions (10.2% vs 5.0%, p=0.002). Patients who had smaller tonsils (grades 1, 2) experienced more frequent bleeding episodes compared to grades 3 and 4 tonsils (10.6% vs 5.5%, p=0.002). Patients receiving postoperative NSAIDs were more likely to have a tonsil bleed than those given paracetamol (13.9% vs 6.3%, p<0.001). Patients who were operated on by attendings had more frequent bleeding episodes compared to those operated on by resident doctors (14.4% vs 7.4%, p=0.049) (Table 1).

**Table 1.** Association of variables with post-tonsillectomy hemorrhage

| | **Post-tonsillectomy hemorrhage** | | | | | |
|---|---|---|---|---|---|---|
| | | **Univariate** | | | **Multivariate** | |
| | **No. of patients (%)** | **Yes (%)** | **No (%)** | **p-value** | **OR (95% CI)** | **p-value** |
| Total | 1,082 (100) | 87 (8) | 995 (92) | | | |
| **Age** | | | | | | |
| <6 | 431 (39.8) | 15 (3.5) | 416 (96.5) | | | |
| 7-15 | 359 (33.3) | 17 (4.7) | 342 (95.3) | 0.37 | | |
| >15 | 292 (26.9) | 55 (18.8) | 237 (81.2) | <0.001 | 15.41 (7.49-31.71) | <0.001 |
| **Sex** | | | | | | |
| Male | 607 (56.1) | 49 (8.1) | 558 (91.9) | | | |
| Female | 475 (43.9) | 38 (8.0) | 437 (92.0) | 0.96 | | |
| **Indication for surgery** | | | | | | |
| Recurrent tonsillitis | 625 (57.8) | 64 (10.2) | 561 (89.8) | | | |
| Airway obstructions | 457 (42.2) | 23 (5.0) | 434 (95.0) | 0.002 | 0.71 (0.41-1.25) | 0.24 |
| **Grade of tonsil size** | | | | | | |
| Smaller (grade 1, 2) | 536 (49.5) | 57 (10.6) | 479 (89.4) | | | |
| Larger (grade 3, 4) | 546 (50.5) | 30 (5.5) | 516 (94.5) | 0.002 | 1.00 (0.59-1.69) | 0.99 |
| **Dissection technique** | | | | | | |
| Cold steel | 717 (66.3) | 52 (7.3) | 665 (92.7) | | | |
| Bipolar forceps | 365 (33.7) | 35 (9.6) | 330 (90.4) | 0.18 | | |
| **Postoperative analgesia** | | | | | | |
| Paracetamol | 837 (77.4) | 53 (6.3) | 784 (93.7) | | | |
| NSAIDs | 245 (22.6) | 34 (13.9) | 211 (86.1) | <0.001 | 0.23 (0.12- 0.47) | <0.001 |
| **Grade of surgeon** | | | | | | |
| Residents | 985 (91.0) | 73 (7.4) | 912 (92.6) | | | |
| Attendings | 97 (9.0) | 14 (14.4) | 83 (85.6) | 0.0049 | 1.70 (0.86-3.34) | 0.123 |
| **Season of surgery** | | | | | | |
| Summer-spring | 675 (62.4) | 56 (8.3) | 619 (91.7) | | | |
| Autumn-winter | 407 (37.6) | 31 (7.6) | 376 (92.4) | 0.69 | | |

NSAIDs: Non-steroidal anti-inflammatory drugs, OR: Odds ratio, CI: Confidence interval

Multivariable analyses identified that age >15 years and receiving postoperative NSAIDs were independent risk factors for PTH (OR: 15.5, 95% CI), 7.68-31.27, p<0.001, and OR: 0.22, 95% CI, 0.11-0.44, p<0.001, respectively) (Table 1).

**Characteristics of PTH**

Of the 87 patients with PTH, no active bleeding was observed in 50 patients (57.5%), including 31 patients aged >15 years (62.0%). These patients had a history of hemorrhage at home, but oropharyngeal examination at the initial presentation revealed normal findings (grade 1 bleeding, 10 patients, 20%) or only a blood clot (grade 2 bleeding, 40 patients, 80%) in the tonsillar fossa without venous oozing or arterial bleeding. These patients were admitted for inpatient observation (conservative treatment group).

The remaining 37 (42.5%) patients [24 were >15 years (64.8%)] with active bleeding (either with venous oozing or arterial bleeding, grade 3 and 4 bleeding, respectively) underwent surgical hemostasis in the OR (operative treatment group).

At presentation with bleeding, the median postoperative day was six days (range, 1 to 17 days). The mean postoperative days for the conservative and operative treatment groups were 7.43 and 5.21 days, respectively (p=0.004).

The median initial hemoglobin level was 13.1 g/dL at the time of presentation with PTH. There were no significant differences between those conservatively treated and those managed with operative exploration (median 12.8 vs 12.9 g/dL, p>0.05).

Overall, children younger than school age (≤6 years) and children at the school age (7-15 years) were 5.3 and 4 times, respectively, less likely to have all bleeding episodes compared to adults.

About one out of every 60 children (1.5%) had important oropharyngeal bleeding, whereas every 12$^{th}$ (8.2%) patient aged >15 years had severe hemorrhages that warranted surgical hemostasis in the OR (p<0.001).

**Rebleeding After Initial Management**

Rebleeding episodes occurred in 18 out of 87 patients (20.6%). Among the patients who were observed after the first bleeding episode (n=50), about one out of every 19 children (5.3%) and every third adult (35.4%) experienced rebleeding (p=0.022). Of the 11 patients with a normal examination on admission, three (1 child, 2 adults) had rebleeding and were once again managed conservatively. Regarding the subset of patients with a clot in the tonsillar fossa, none of the children (n=13) had a recurrent bleeding episode, whereas 9/26 adults (35%) had rebleeding [4 (15.3%) needed surgical intervention in the OR] (p<0.01).

Of the 37 patients initially managed for active bleeding in the OR, six (16.2%) (including one child and five adults) experienced rebleeding. Of these, the child and two adults underwent a second surgical procedure to control the rebleeding episodes (Table 2).

The median rebleeding day after the initial bleeding episodes was four (range, 1-6). Similarly, the median rebleeding day was four (range, 3-6) in patients who needed surgical hemostasis for oropharyngeal bleeding. The characteristics of rebleeding patterns are shown in Table 3.

## Discussion

The literature contains many ways of describing and labeling PTH. Although the frequency of readmissions or reoperations to control hemorrhage was reported generally to be below 5% in the literature, the frequency increased up to 20% when patients with minor bleedings (not requiring intervention) were included in the cohorts. In the presented study, we observed that the overall PTH risk was 8.0% (all forms of presentations) for all age groups. Considering bleeding episodes that necessitated surgical intervention, the overall PTH risk was 3.5% in our cohort which is parallel to the previous reports (9,10).

**Table 2.** Hemorrhage classification according to the intensity of bleeding

| | Bleeding | | | Rebleeding | | | |
|---|---|---|---|---|---|---|---|
| | **No. of patients (%)** | **≤15 years of age (%)** | **>15 years (%)** | **≤15 years of age (%)** | **>15 years (%)** | **Post-op day (mean)** | **Hb g/dL** |
| **Non-active bleeding** | | | | | | | |
| **Total** | 50 (57.5) | 19 (37.5) | 31 (62.5) | | | | |
| **Clot (-)** | 11 (11.5) | 6 | 5 | 1 | 2 | | |
| **Clot (+)** | 39 (46.0) | 13 (33) | 26 (66) | 0 (0) | 9 (35) | 7.43 | 12.8 |
| **Active bleeding** | | | | | | | |
| **Venous Oozing/ Arterial brisk** | 37 (42.5) | 13 (35) | 24 (65) | 1 (7) | 5 (21) | **5.21 (p=0.004)** | 12.9 |

Hb: Hemoglobin, g/dL: grams per deciliter

**Table 3.** Characteristics of rebleeding episodes

| Patient number | Age | Day of first bleeding | Severity of first bleeding* | Surgical homeostasis for the first bleeding | Severity of second bleeding* | Day of second bleeding (after the first bleeding) | Surgical homeostasis for the second bleeding |
|---|---|---|---|---|---|---|---|
| 1 | 23 | 5 | 3 | Yes | 3 | 5 | Yes |
| 2 | 24 | 5 | 2 | No | 3 | 4 | Yes |
| 3 | 45 | 1 | 3 | Yes | 2 | 6 | No |
| 4 | 18 | 9 | 2 | No | 2 | 4 | No |
| 5 | 8 | 4 | 1 | No | 1 | 1 | No |
| 6 | 19 | 1 | 4 | Yes | 4 | 5 | Yes |
| 7 | 28 | 6 | 2 | No | 3 | 3 | Yes |
| 8 | 38 | 10 | 3 | Yes | 2 | 6 | No |
| 9 | 24 | 7 | 2 | No | 4 | 6 | Yes |
| 10 | 38 | 5 | 2 | No | 2 | 2 | No |
| 11 | 7 | 10 | 4 | Yes | 3 | 4 | Yes |
| 12 | 31 | 1 | 4 | Yes | 2 | 5 | No |
| 13 | 36 | 8 | 2 | No | 1 | 2 | No |
| 14 | 24 | 6 | 2 | No | 1 | 3 | No |
| 15 | 34 | 8 | 1 | No | 1 | 6 | No |
| 16 | 27 | 6 | 2 | No | 4 | 4 | Yes |
| 17 | 48 | 7 | 1 | No | 1 | 5 | No |
| 18 | 30 | 3 | 2 | No | 1 | 4 | No |

*Severity of bleeding "1: Normal oropharyngeal exam, 2: Clot in tonsillar fossa without active bleeding, 3: Venous oozing, 4: Arterial brisk hemorrhage

Numerous studies have examined and found various risk factors for PTH including age, gender, surgical technique, surgeon's skill level, and tonsillectomy indication. Our univariate findings revealed that together with older age (>15 years), also the infectious indication, smaller tonsils, use of NSAIDs for pain relief after tonsillectomy, and tonsillectomies performed by attendings were associated with higher rates of PTH.

In the presented study, both the frequency and the severity of postoperative hemorrhage varied significantly among the age groups. The PTH risk (for all presentations) was 4.0% in children, whereas the risk was 4.7 times higher (18.8%) in adults. Similarly, when we consider only the patients undergoing surgical hemostasis, the rate of return to the OR was 1.6% for children and 8.5% for adults (5.3 times higher odds). As reported in previous reports, older age was consistently more associated with an increased risk of hemorrhage. Lee et al. (11) reported that the odds of having PTH were six times higher (0.5% vs 3.2%) in patients aged ≥12 years than in those patients aged <12 years. In a study by Tomkinson et al. (12) patients aged ≥12 years were 3.3 times more likely to have a secondary PTH than patients <12 years of age. Regarding tonsillectomy indication, many studies showed that patients with chronic tonsillitis are more likely to have PTH than patients with hypertrophic tonsils (9, 13, 14). Our univariate results support this finding. Recurrent and chronic inflammation may result in tissue adhesion and make tonsils dense, more fibrous, and smaller, and all can lead to difficulty in dissection from the tonsil bed. Furthermore, we found a relationship between the surgeon's skill level and hemorrhage. Univariate analysis revealed that the surgeries performed by attendings were associated with a higher risk of hemorrhage than those performed by resident doctors, as also described by Sarny et al. (6).

NSAIDs such as ibuprofen increase post-tonsillectomy bleeding. Although many studies have revealed that bleeding time does not change in patients using NSAIDs, recent meta-analyses have shown that particularly postoperative NSAIDs administration was associated with bleeding (15-18). Riggin et al. (17) concluded that in the general population (children and adults) NSAIDs affected the risk of bleeding if given only postoperatively. In our study, patients who received NSAIDs for pain control postoperatively had a two-fold bleeding risk than patients using paracetamol.

When, however, the variables significant in the univariate analysis were taken into account to reveal the independent predictors of PTH by multivariate logistic regression analysis, older age, and postoperative NSAID use came forth as significant risk factors for PTH (all presentations) with OR=15.5 and OR=0.22, respectively. In a few studies involving both adults and children, risk factors for PTH were calculated by logistic regression to get simultaneous coverage of all influencing factors (6, 11,12).

Rebleeding is another problem of PTH. Of the 87 patients with PTH, 18 (20.6 %) experienced a second bleeding episode which was also similar to the results of a large community-based database. In the presented study, we observed that about one out of every 6-7 adults (4/26) with clots in the tonsillar fossa at the initial presentation experienced rebleeding during hospitalization and were taken to the OR to control the bleeding. However, no rebleeding was observed in any of the children with blood clots in the tonsillar fossa. Three out of 11 patients (one out of 6 children and two out of five adults) with normal examination findings had bleeding and all were conservatively managed. In the literature, a few reports addressed the severity of rebleeding episodes in patients with PTH. A previous study (including patients <20 years of age) by Sethi et al. (18) reported that 46.3% of the patients presenting with a blood clot in the tonsillar fossa had rebled and returned to the OR, whereas 18.5% of the patients presenting without a blood clot rebled. Sarny et al. (6), conducting a study including children and adults, reported that severe hemorrhage had occurred following minor hemorrhage in 10.2% of the patients with PTH. However, the authors did not specify how many patients in the cohort with severe bleeding had normal oropharyngeal examination and how many had clots. This rebleeding rate was consistent with our results, as 8.0% of our patients with non-active bleeding at presentation experienced a severe rebleeding episode during follow-up. Whelan et al. (8) reported the results of a pediatric cohort, in which the severity of hemorrhage was classified similar to ours. Of the 130 patients who presented with a history of blood-tinged sputum and normal physical examination, 10.2% later had rebleeding episodes. Of the 94 patients with blood clots but no active bleeding, 17.3% experienced rebleeding. However, the children presenting with clots but having no active bleeding did not rebleed in our study. Similar to ours, few studies have also reported lower rates of rebleeding in patients with a normal oropharyngeal examination. They all classified a clot in the tonsillar fossa as a major risk for hemorrhage or active rebleeding. Peterson and Losek (19) noted that there was no recurrence of bleeding in the 14 pediatric patients who had an initial normal examination. In the pediatric cohort of Arora et al. (7), only two patients (4.7%) with a normal oropharyngeal examination experienced a second bleeding episode.

We also showed that the second bleeding episodes (either severe or all cases) medially occurred on the 4$^{th}$ day after the first bleeding. Similarly, Attner et al. (10) reported that the second rebleeding episode medially occurred on the 3$^{rd}$ day (range, 0-14). Conversely, Sarny et al. (6) reported that almost half of the second severe bleeding episodes had occurred on the day after the minor hemorrhage episodes.

The presented study has notable limitations. Its retrospective nature makes it difficult to control for various confounders. For example, because intraoperative details were not consistently available in operative reports, we could not assess the correlations between the degree of difficulty in surgery or intraoperative blood loss and the risk of postoperative bleeding.

## Conclusion

In conclusion, adult age, and the use of postoperative NSAIDs were found to be independent clinical risk factors for PTH in the presented study. Besides, adult patients who presented without active bleeding showed an increased risk of developing severe rebleeding compared to children. Any of the children with a blood clot in the tonsillar fossa did not experience any form of rebleeding, whereas one out of three adults with blood clots rebled, and almost half of them underwent surgical homeostasis in the OR. In light of these findings, we conclude that adult patients are at greater risk of PTH than younger patients.

### Ethics

**Ethics Committee Approval:** This study was reviewed and approved by the Institutional Review Board of Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital (approval no: 53/11, date: 06.08.2018)

**Informed Consent:** Informed consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data.

### Footnotes

### Authorship Contributions

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

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

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

**Main Points**

- Adult age and the use of postoperative NSAIDs are found to be independent clinical risk factors for PTH.
- The PTH risk (for all presentations) was 4.0% in children, whereas the risk was 4.7 times higher (18.8%) in the adult population.
- For patients undergoing surgical hemostasis, the rate of return to the operating room is 1.6% for children and 8.5% for adults (5.3 times higher odds).
- Adult patients who presented without active bleeding showed an increased risk of developing severe rebleeding compared to children.
- The evidence of minor/light bleeding increased the risk of a second bleeding episode.

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# Endoscopic Sphenopalatine Artery Cauterization Under Local Anesthesia for Posterior Epistaxis: A Prospective Cohort Study of its Tolerability and Efficacy

Original Investigation

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**Abstract**

**Objective:** To assess the tolerability and efficacy of endoscopic sphenopalatine artery cauterization (ESPAC) under local anesthesia (LA) in managing posterior epistaxis.

**Methods:** It was a prospective, cohort study, conducted in the Otorhinolaryngology Department of a tertiary-level hospital. Patients aged 18 years or above with posterior epistaxis who underwent ESPAC under LA were included. The tolerability of the procedure was reflected by the intraoperative pain measured using an 11-point numerical rating scale while the rebleed rate up to three months postoperatively denoted its efficacy.

**Results:** A total of 35 patients, 23 males and 12 females, aged 31 to 86 years (mean 57.42 ± 12.94) were included. Five out of 35 (14.2%) patients needed additional procedures besides ESPAC; 82.8% (29/35) had pterygopalatine fossa (PPF) block before ESPAC. The numerical rating scale reflecting the intraoperative pain ranged from 1 to 7 with a mean of 3.6 (± 1.7). The mean score was slightly higher in females than in males. Similarly, those who did not receive PPF block had a higher mean score than those who received it; however, the differences were not statistically significant. Meanwhile, the mean score was the same (3.6) irrespective of any additional procedure besides ESPAC. Amongst the 30 patients who completed the three-month follow-up, two patients rebled, so the overall success rate amounted to 93.3% in three months.

**Conclusion:** Based on the outcome of this study, ESPAC under LA for posterior epistaxis is well tolerated and is as efficacious as under general anesthesia.

**Keywords:** Epistaxis, endoscopic surgical procedure, local anesthesia, pterygopalatine fossa, cautery, pain

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***Cite this article as:*** *Gurung U, Thapa N, Khadgi S. Endoscopic Sphenopalatine Artery Cauterization Under Local Anesthesia for Posterior Epistaxis: A Prospective Cohort Study of its Tolerability and Efficacy. Turk Arch Otorhinolaryngol. 2024; 62(3): 88-94*

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**Received Date:** 06.05.2024
**Accepted Date:** 12.09.2024

DOI: 10.4274/tao.2024.2024-5-2

## Introduction

Posterior epistaxis accounts for 5-10% of all epistaxis usually affecting the elderly with the sphenopalatine artery as the major contributor (80%) (1,2). Owing to its posterior location, it is difficult to localize and control with anterior rhinoscopy (1-3). Endoscopic sphenopalatine artery ligation (ESPAL) or cauterization has recently gained preference over the traditional nasal packing (NP) as first-line management for posterior epistaxis

mostly due to its high efficacy ranging from 76% to 100%, reduced morbidity including pain, shorter hospital stay and subsequently reduced cost (1-5).

Endoscopic sphenopalatine artery cauterization (ESPAC) is generally performed under general anesthesia (GA) (2,3,6). However, this can be unsafe for those patients with high anesthetic risk. Under such conditions, prolonging NP or embolization has been suggested; however, these procedures have lesser success rates of 62% and 75 %, respectively, and are not without complications (2,7,8). Hence, considering ESPAC under LA is an alternative for posterior epistaxis (8). There are only a handful of studies that have demonstrated the success of this procedure under LA (5,9,10). This is the only prospective study with a fairly large number of ESPAC performed under LA. It assesses the tolerability of ESPAC under LA and its efficacy in controlling posterior epistaxis.

## Methods

This is a prospective cohort study of 35 patients who underwent ESPAC under LA. Ethical approval was obtained from the Institutional Review Committee of Tribhuvan University Teaching Hospital – Maharajgunj Medical Campus prior to the study [date: 22.09.2019, ref: 133/(6-11) E²/076/077]. All patients were informed about the objective of the study and signed the written consent form.

The sample size was calculated based on the prevalence of ESPAC for posterior epistaxis (2.3%) taking a 5% margin error. Patients aged 18 years or above presenting to the Otorhinolaryngology Department of a tertiary-level hospital with posterior epistaxis were included. Patients with post-traumatic epistaxis, bleeding nasal mass, previous nasal surgery including ESPAC, bleeding disorder, and anxiety disorder were excluded. ESPAC was offered to patients with posterior epistaxis confirmed on nasal endoscopy; with two or more bleeding episodes in the last two weeks or active bleeding needing nasal packing at the time of hospital admission. The department had a low threshold for offering ESPAC for posterior epistaxis due to the limited healthcare facilities in the country providing services for epistaxis and the difficulty for patients from distant areas to visit the hospital regularly. The procedures were performed between October 2019 to January 2022 with a gap of ten months between March 2020 to January 2021 due to the Coronavirus disease-2019 (COVID-19) pandemic.

A day before surgery, the patients were verbally explained about the procedure ESPAC to be performed under LA. Patients were shown the 11-point numerical rating scale (NRS) that would be used to rate the severity of pain they could experience intraoperatively the next day, and explained how totally the severity of pain with the numbers on a scale of 0 "no pain" to 10 "the worst pain imaginable". Premedication using an intramuscular injection of pethidine (1 mg/kg) and promethazine (0.5 mg/kg) was given half an hour before the procedure in the preoperative room as per the department policy. After the patient was transferred to the operating theater, an ipsilateral pterygopalatine fossa (PPF) block was given via the greater palatine foramen (GPF). The depression of the foramen was palpated intra-orally on the hard palate medial to the third molar as recommended by previous studies (5,11). 2 mL of 2% lidocaine with 1:2,00,000 adrenaline was infiltrated through the GPF to the PPF with subsequent blanching of the hard palate. A 25-gauze needle bent at 2.5 cm from the tip at an angle of 45 degrees was used for the PPF block based on the configuration of the needle advocated by a cadaveric study (12). Aspiration before infiltration was done to avoid inadvertent infiltration into any vessel (Figure 1).

For ESPAC, the patient was placed in reverse Trendelenburg position with a 15-degree head elevation. The nasal cavity including the middle meatus was decongested and anesthetized topically using pieces of Merocel® (Medtronic Inc., Minneapolis, MN, USA) impregnated with a mixture of 1 mL of 1:1000 adrenaline in 30 mL 4 % lidocaine. Further, the posterior part of the middle meatus was infiltrated under endoscopic guidance with 2 mL of 2% lidocaine with 1:2,00,000 adrenaline using a 22-gauze spinal needle. In case septoplasty was needed, the septum was infiltrated on both sides. A piece of Merocel® (Medtronic Xomed, Jacksonville, FL, USA) secured with a thread was placed snuggly at the choana to prevent any local anesthetic or blood from tricking into the throat.

A curvilinear incision was made on the lateral wall of the middle meatus around 1 cm anterior to the posterior end of the middle turbinate. Middle meatal antrostomy was done where landmarks were unidentifiable. The mucoperiosteal flap was raised until the crista ethmoidalis (CE) was visualized. The SPA located posterior to CE exiting the sphenopalatine foramen was cauterized using bipolar cautery set at 20 watts (Figure 2). The mucoperiosteal flap was repositioned and

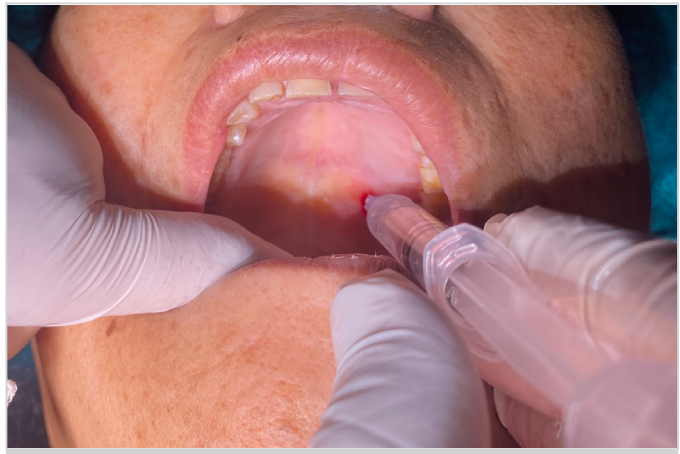

**Figure 1.** Left pterygopalatine fossa block

an absorbable gelatin sponge piece was placed on top. Nasal packing was not done. Patients were discharged the following day if no further nose bleeding occurred. Oral antibiotics, analgesics, and topical decongestants were prescribed for a week and gentle saline douching was advised for two weeks.

The outcomes measured were tolerability and efficacy of the procedure.

### Tolerability

This was assessed by intraoperative pain. Two hours postoperatively, patients were asked to fill out the NRS to rate the intraoperative pain. This was to allow pethidine to wear off and also avoid recall bias. Bleeding, hard palate numbness, or other complications, if any, were noted.

### Efficacy

The rebleed rate reflected efficacy. Patients were followed-up in two weeks and three months or when rebleeding occurred. At the two-week follow-up, patients were assessed for rebleeding or hard palate numbness. At three months, patients were followed up by telephone or in person for any bleeding.

### Statistical Analysis

The data was entered in Microsoft® Excel (Version 16.72) The descriptive data were presented in range, mean, and standard deviation, and the inferential statistics in unpaired t-test.

## Results

Eighteen of the 35 patients underwent ESPAC between October 2019 and February 2020. The procedure had to be discontinued due to COVID-19 until routine ESPAC was resumed. The remaining 17 patients underwent ESPAC between January 2021 to January 2022.

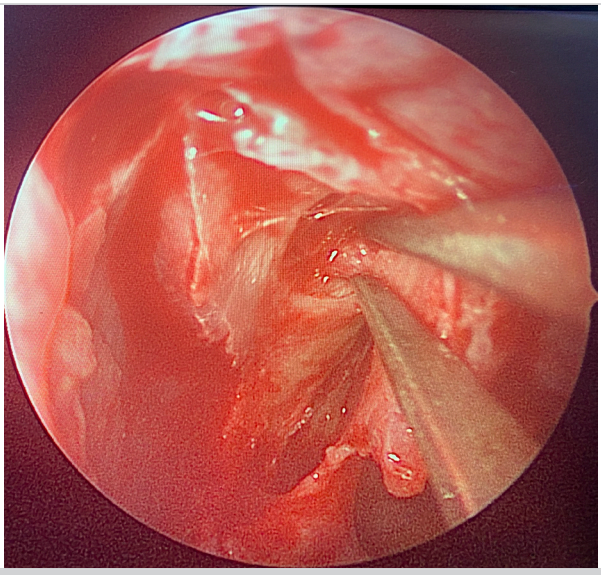

**Figure 2.** Sphenopalatine artery located exiting the sphenopalatine foramen posterior to crista ethmoidalis

The ages of the patients ranged from 31 to 86 years, with the mean age being 57.42 (±12.94) years. Males were nearly twice as many as females (1.9:1). Hypertension was the most common comorbidity. All patients except one had unilateral bleeding. Most patients (23/35) had nasal packing on an average of 3.45 (±1.28) days (range 1-7 days) before ESPAC. Five out of 35 (14.2%) patients needed additional procedures besides ESPAC. While 82.8% (29/35) had PPF block before ESPAC, the remaining six did not due to difficulty locating GPF (Table 1).

None of the patients had their procedure abandoned owing to intraoperative bleeding, intolerable pain, or adverse effects of LA with adrenaline.

### Outcomes

### Tolerability-Intraoperative Pain

The overall NRS score ranged from 1 to 7 with a mean of 3.6 (±1.7). The mean score was slightly higher in females than in males. Similarly, those who did not receive PPF block had a higher mean score than those who received it; however, the differences were not statistically significant. Meanwhile, the mean score based on the surgical procedure was the same irrespective of any additional procedure besides ESPAC (Table 2). None of the patients had an alteration in the hard palate sensation in the immediate postoperative period or the two-week follow-up.

### Efficacy-Rebleed Rate

Initially, all patients were followed-up up to two weeks; however, five were lost to follow-up at the third month. Two patients rebled; one, on postoperative day two and another after a month postoperatively. The first patient was managed with nasal packing whilst the second was managed conservatively. Both had only unilateral ESPAC. Excluding the drop-outs, the overall success rate of ESPAC in three months was 93.3% (28/30).

## Discussion

Epistaxis commonly affects elderly patients who tend to have multiple comorbidities which increases anesthetic risk (5,9). This was echoed in this study also with the mean age of the patients being 58.34 (±12.9) years and most of them (30/35) having comorbidities, predominantly hypertension. Elderly patients with coronary atherosclerosis are unlikely to tolerate systemic hypotension induced by GA needed for bloodless surgical fields. Hence, considering LA with vasoconstrictors is an alternative to control local bleeding without inducing

systemic hypotension, avoiding the risk related to GA (5). Several studies predominantly on dental or oral procedures have assessed the safety of LA with vasoconstrictors in cardiovascular-compromised patients. The judicious use of LA with vasoconstrictors has been found relatively safe in this category of patients (13-15).

Various nasal procedures like cosmetic or reconstructive surgery, polypectomy, turbinectomy, nasal bone fracture

**Table 1.** Demographics of patients (n=35)

| | | | Number of patients |
|---|---|---|---|
| Gender | Male | | 23 |
| | Female | | 12 |
| Comorbidities | Hypertension | | 17 |
| | Hypertension with | Diabetes mellitus | 4 |
| | | Diabetes mellitus and hypothyroidism | 1 |
| | | Rheumatoid arthritis | 1 |
| | | Alcohol withdrawal syndrome | 1 |
| | Alcoholic hepatitis | | 2 |
| | COPD | | 3 |
| | Peripheral vascular disease | | 1 |
| | None | | 5 |
| Side of bleeding | Right | | 18 |
| | Left | | 16 |
| | Bilateral | | 1 |
| Type of nasal packing | Rapid Rhino® (Smith & Nephew, Andover, MA, USA) | | 18 |
| | Gelatin sponge | | 3 |
| | Merocel® (Medtronic Xomed, Jacksonville, FL, USA) | | 2 |
| | None | | 12 |
| Type of procedure | Unilateral ESPAC | | 30 |
| | Unilateral ESPAC with | Septoplasty | 2 |
| | | Middle meatal antrostomy | 1 |
| | | Septoplasty and middle meatal antrostomy | 1 |
| | Bilateral ESPAC with septoplasty | | 1 |
| PPF block | Given | | 29 |
| | Not given | | 6 |

COPD: Chronic obstructive pulmonary disease, ESPAC: Endoscopic sphenopalatine artery cauterization, PPF: Pterygopalatine fossa

**Table 2.** Severity of intraoperative pain (n=35)

| | 11-point Numerical Rating Scale | | |
|---|---|---|---|
| | Range | Mean (SD) | p-value |
| Gender | | | |
| Male (23) | 1-7 | 3.4 | 0.634 |
| Female (12) | 2-6 | 3.7 | |
| Additional PPF block | | | |
| Overall (35) | 1-7 | 3.6 (±1.7) | |
| Given (29) | 1-7 | 3.6 (±1.7) | 0.053 |
| Not given (6) | 3-7 | 3.8 (±1.7) | |
| Surgical procedures (n) | | | |
| ESPAC only (30) | 1-7 | 3.6 (±1.6) | 0.42 |
| ESPAC with others (5) | 2-7 | 3.6 (±1.7) | |

SD: Standard deviation, ESPAC: Endoscopic sphenopalatine artery cauterization, PPF: Pterygopalatine fossa

**Table 3.** Comparison of the outcomes of ESPAC/ESPAL in different studies

| Author and publication year | Number of patients | Type of anesthesia | Type of surgery | Follow-up in months | Success rate (%) |
|---|---|---|---|---|---|
| Jonas et al. (5) 2010 | 2 | LA infiltration and PPF block without sedation | ESPAL – 1<br>With AEA - 1 | 3 | 100 |
| Soyka et al. (8) 2011 | 36 | GA | ESPAL - 31<br>With AEA - 5 | 1 | 97 |
| Yung et al. (9) 2016 | 21 | Topical LA without sedation | ESPAC - 21 | 3 | 76 |
| İsmi et al. (3) 2016 | 30 | GA | ESPAL - 30 | 6-30 (mean 15) | 90 |
| Sireci et al. (2) 2018 | 8 | GA | ESPAC | 6 | 100 |
| Hervochon et al. (6) 2018 | 83 | GA | ESPAC<br>Unilateral- 36<br>Bilateral- 47 | 1 | Unilateral- 75%<br>Bilateral- 91.5 |
| Galili et al. (7) 2021 | 76 | GA | ESPAC+ ESPAL | 1 month | 92.1 |

LA: Local anesthesia, GA: General anesthesia, PPF: Pterygopalatine fossa, ESPAL: Endoscopic sphenopalatine artery ligation, AEA: Anterior ethmoidal artery, ESPAC: Endoscopic sphenopalatine artery cauterization

reduction, and small tumor resection have been performed under local or regional anesthesia with good intraoperative conditions and patient tolerance (16).

In our study, intramuscular pethidine and promethazine were administered before LA into the PPF and the middle meatus. Preemptive light sedation has been found to facilitate anesthetic and surgical procedures by alleviating anxiety, which reflects on patient satisfaction (16).

PPF block using local anesthetic and vasoconstrictor via the greater palatine canal serves two purposes pertinent to nasal surgery (5). It causes vasospasm of the third part of the maxillary artery ultimately reducing blood flow to the SPA. It also blocks the terminal branches of the maxillary nerve hence anesthetizing the lateral nasal wall and posterior part of the septum supplied by the nasopalatine nerve and posterior nasal branches of the maxillary artery (5). PPF block as an add-on to GA has been reported to reduce intraoperative bleeding during endoscopic sinus surgery without any complication and also lower early post-operative pain after endonasal surgery (17,18). Jonas et al. (5) reported successfully treating two posterior epistaxis cases, a 20-year-old with cystic fibrosis and a 44-year-old with post-head injury stroke with ESPAL and anterior ethmoidal artery ligation for the second patient under PPF block, without sedation as they were deemed unfit for GA. Probable complications of this block are intravascular injection, infraorbital nerve injury, and anesthesia or injury of the orbital nerves (12). Fortunately, none of our patients who received PPF block had any of these complications. Emergency ESPAC by Yung et al. (9) in 21 patients under topical LA using 0.75 mL of 25% cocaine paste without sedation was tolerated well. Therefore, good local or regional anesthesia has been considered a suitable alternative to GA to perform ESPAC (8).

NRS, a reliable scale for self-evaluation of acute pain was used to evaluate the intra-operative pain in this study (19). The pain rating relates to the measure of satisfaction with the degree of analgesia. The value "4" is usually interpreted as meeting the patient's goal for anesthesia (20). Based on the correlation of NRS with objective pain score (OPS) for acute postoperative pain, where OPS "1" and "2" mean inadequate analgesia needing rescue analgesia in the form of fentanyl and "3" means adequate analgesia with the implementation of paracetamol as rescue analgesia, whilst "4" means adequate analgesia needing no intervention, NRS 2-5 equates to OPS 3 and NRS ≥ 6 equates to OPS 1 and 2 (21). In our study, the mean NRS score was 3.6, which indicated the degree of analgesia offered during the procedure was adequate. It remained almost similar irrespective of gender, additional nasal procedure, or PPF block. This pain score is comparable to the median visual analog scale amounting to 3 for ESPAC under GA in the prospective study by Nikolaou et al. (22) where the pain scale was compared amongst 61 patients (45 with anterior epistaxis, 16 with posterior epistaxis) for Rapid Rhino (RR) (Smith & Nephew, Andover, MA, USA) packing, surgery, and balloon packing. The pain scale reflecting the discomfort during or after the procedure, recorded in the consequent postoperative outpatient visit was less for ESPAC (3) as compared to RR packing (6) and balloon packing (7.5). In a two-cycle audit, Yung et al. (9) assessed the discomfort on a 5-point scale on 21 patients for emergency ESPAC under topical LA. The mean intraoperative discomfort scale improved from 3.2 to 1.6 in the second audit after incorporating changes like placing a temporary tampon at choana and local anesthetics in the vicinity of SPA, respectively, based on feedback from the previous audit. None of the procedures were abandoned or converted to GA due to technical difficulties or patient intolerance in their study as observed in our study also.

The success rate of ESPAC in three months in our study was 93.3% (28/30). This is on par with other studies (Table 3) (2,3-5). Of the two patients who rebled, one was managed conservatively and the other with nasal packing. None of them needed revision ESPAC. Although the exact cause of rebleeding in our study was not known, rebleeding post-ESPAC can occur due to various reasons. The likely reasons could be due to the existence of more than one branch of the SPA while it exits from the foramen, failure to clip or cauterize the posterior septal branch, presence of collateral vessels or slippage of clips, or accompanying anterior ethmoid artery bleeding (3).

The likely complications of ESPAC include increased nasal crusting, palatal numbness septal perforation, and partial middle turbinate necrosis in the case of bilateral ESPAC (2, 5, 6). Although nasal crusting was common, more so due to nasal packing, none of the patients in our study had any other complications.

The strength of this study includes the inclusion of a large series of patients who underwent ESPAC under LA. The limitation of recall bias for intraoperative pain was overcome by assessing the pain after two hours of the procedure. Although multiple surgeons were involved, all of them followed the same protocol. Six patients did not receive PPF block due to difficulty locating GPF consequent to probable anatomical variation however this did not alter the main outcome (11).

## Conclusion

Based on the outcome of this study, ESPAC under LA for posterior epistaxis is well tolerated and is as efficacious as under general anesthesia. Performing ESPAC under LA routinely is apt for resource-constrained healthcare setups with limited GA slots not only for patients with higher anesthetic risk but also for otherwise healthy patients. This will help prevent a backlog of patients needing ESPAC.

### Ethics

**Ethics Committee Approval:** This is a prospective cohort study of 35 patients who underwent ESPAC under LA. Ethical approval was obtained from the Institutional Review Committee of Institute of Medicine, Tribhuvan University prior to the study [date: 22.09.2019, ref: 133/(6-11) E2/076/077].

**Informed Consent:** All patients were informed about the objective of the study and signed the written consent form.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: U.G., N.T., Concept: U.G., Design: U.G., N.T., S.K., Data Collection and/or Processing: U.G., N.T., S.K., Analysis and/or Interpretation: U.G., N.T., S.K., Literature Search: U.G., N.T., S.K., Writing: U.G., N.T., S.K.

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

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

**Main Points**

- Endoscopic sphenopalatine artery cauterization (ESPAC) is generally performed under general anesthesia (GA). Only a few studies have explored the possibility of performing it under local anesthesia (LA), especially for patients deemed unfit for GA.
- In this cohort study, the tolerability of the procedure under LA was assessed in 35 and efficacy in 30 patients. This is the largest cohort of this kind.
- The main outcomes, tolerability were assessed by numerical rating scale (NRS) pain score and the efficacy by rebleeding rate in three months.
- The procedure was well tolerated under LA and had a success rate on par with published literature assessing its efficacy under GA.
- This study supports the feasibility of performing ESPAC under LA not only on high-risk GA cases but also on a routine basis and can be opted as a better first-line management option than

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# Angiotensin-Converting Enzyme Insertion/Deletion Gene Polymorphism in Chronic Rhinosinusitis with Nasal Polyps

Original Investigation

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## Abstract

**Objective:** Inflammatory processes play a role in the etiopathogenesis of chronic rhinosinusitis. Many gene polymorphisms have been associated with inflammation. In this study, we aimed to examine the relationship between angiotensin-converting enzyme insertion/deletion gene polymorphism and chronic rhinosinusitis.

**Methods:** Fifty-two cases with nasal polyps and 139 control patients were included in the study. Angiotensin-converting enzyme insertion/deletion gene polymorphisms, genotype, and allele distributions were determined. Results were statistically compared between groups.

**Results:** Statistically significant differences were found between the chronic rhinosinusitis with nasal polyps group and the control group in terms of genotype and allele distribution (p=0.015, 0.003, respectively). There were no significant differences in genotype distribution in the chronic rhinosinusitis with nasal polyps group in terms of non-steroidal anti-inflammatory drug (NSAID) allergy, asthma, and NSAID-exacerbated respiratory disease (p=0.645, 0.660, 0.095, respectively).

**Conclusion:** We observed that the risk of chronic rhinosinusitis is higher in individuals with the deletion-deletion genotype and D allele of the angiotensin-converting enzyme insertion/deletion gene polymorphism. We believe that these results could be related to the high angiotensin-converting enzyme levels in these patients.

**Keywords:** Sinusitis, nasal polyps, gene polymorphism, inflammation, angiotensin-converting enzyme, genetic association studies, non-steroidal anti-inflammatory agents

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***Cite this article as:*** *Sivrice ME, Akın V, Yasan H, Hekimler Öztürk K, Kumbul YÇ. Angiotensin-Converting Enzyme Insertion/Deletion Gene Polymorphism in Chronic Rhinosinusitis with Nasal Polyps. Turk Arch Otorhinolaryngol. 2024; 62(3): 95-100*

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**Received Date:** 28.04.2024
**Accepted Date:** 21.08.2024

DOI: 10.4274/tao.2024.2024-4-4

## Introduction

Approximately 25-30% of chronic rhinosinusitis (CRS) patients have nasal polyps, a condition that has been termed CRS with nasal polyps (CRSwNP) (1,2). Although CRSwNP has been known for over three thousand years, its etiopathogenesis has not been clarified. Its prevalence is between 1% and 4%. It is more common in males (1). It presents with symptoms that negatively affect daily life, such as nasal congestion, runny nose, and smell disorders. Its recurrence rates

are high despite the currently available medical and surgical treatments (1,2). Therefore, studies on its etiopathogenesis are important for discovering new treatment strategies.

Angiotensin-converting enzyme (ACE) is secreted from the endothelium. ACE is high in lung and brain capillaries (3). It has many different functions in the nasal mucosa as in many other tissues (4). Its main function is to convert angiotensin I to angiotensin II, a powerful vasopressor involved in fluid and electrolyte homeostasis (3). ACE has also been shown to affect inflammatory processes (5).

Genetic studies on ACE have gained popularity in recent years. The ACE gene is located on chromosome 17q23, and many polymorphisms of this gene have been described (6). The most popular polymorphism of ACE is the insertion/deletion polymorphism (I/D). In this polymorphism, ACE deletion-deletion (DD) and insertion-insertion (II) genotypes are homozygous, while ACE insertion-deletion (ID) genotypes are heterozygous. Insertion in the ACE gene reduces ACE expression. Therefore, people with the ACE DD genotype have greater ACE levels than those with the ID and II genotypes (7,8). A relationship between these polymorphisms and cardiovascular diseases such as atherosclerosis, coronary artery disease, cardiomyopathy, hypertension, preeclampsia, and some malignancies has been found (9-11). Studies about the relationship between the ACE gene and asthma and allergic rhinitis are also present (12,13). There are many studies in literature that have examined the role of various gene polymorphisms in the etiopathogenesis of nasal polyps and CRSwNP. Interleukin-1α (IL-1α), IL-1β, and tumor necrosis factor-α are popular among these gene polymorphisms (14,15). We could not identify any studies examining the CRSwNP and ACE I/D gene polymorphism in the literature. Therefore, we planned to determine the influence of ACE I/D gene polymorphism on CRSwNP.

## Methods

### Patients

The research protocol of this study was approved by the Süleyman Demirel University Faculty of Medicine Clinical Research Ethics Committee Presidency (no: 240, date: 04.09.2020). The study was conducted according to the international ethical standards set by the Declaration of Helsinki. The study was conducted at the Department of Otolaryngology and Medical Genetics Department of Süleyman Demirel University tertiary hospital between September 2020 and September 2021 with 181 patients. Informed consent was taken from each patient. The study group consisted of 52 patients and the control group of 139 patients. The inclusion criteria were: being older than 18 years, having been operated on for CRSwNP, preoperatively assessed with paranasal sinus computed tomography. Patients with predisposing factors such as cystic fibrosis, Kartegener's syndrome, and a history of drug use affecting the renin-angiotensin system, patients with a history of autoimmune disease, patients with systemic chronic inflammatory disease, patients operated on for antrochoanal polyps were excluded. The control group consisted of septoplasty patients over 18 who were not assessed to have chronic sinusitis in preoperative paranasal sinus computed tomography and nasal endoscopy. Patients with a history of autoimmune diseases and patients with systemic chronic inflammatory diseases were not included in the control group. In the study, age, gender, comorbidity, and drug allergy history of the patients were recorded, and ACE I/D polymorphism was analyzed.

### Sampling

During preoperative routine blood tests, four cc of blood was also taken into the tubes with ethylene-diamine-tetraacetic acid for genetic analysis. These blood samples were preserved at -20 ˚C in the genetics laboratory.

### Genotyping

The high pure polymerase chain reaction (PCR) template preparation kit (Roche Applied Science, Germany) provided DNA (deoxyribonucleic acid) samples in accordance with the manufacturer's protocol. The concentration and purity of the samples were adjusted by measuring with a Nanodrop 2000c spectrophotometer (Thermo Scientific, USA). The A260/A280 absorbance ratio for all DNAs was obtained in the range of 1.8-2.0. PCR was used on each DNA sample using ADE gene I/D polymorphism genotype allele-specific primers (forward: TGGAGACCACTCCCATCCTTTCT, reverse: GATGTGGCCATCACATTCGTCAGAT) and the FastStart High Fidelity PCR System dNTPack (Roche Applied Science, Germany) kit. It contains 10 pmol of F and R primers, 1.8 mM $MgCl_2$, 10 mM dNTP mix, 1.25 U Taq polymerase, and 250 ng total genomic DNA for each PCR. The PCR was performed with the following conditions: Ten minutes of pre-incubation at 94 ˚C, 35 cycles at 94 ˚C for 2 minutes, at 57 ˚C for 30 seconds, then at 72 ˚C for 1 minute, and finally at 72 ˚C for 7 minutes. After the PCR, 2% agarose gel electrophoresis was administered and stained with GelRed Nucleic Acid Gel Stain (Biotium, USA). The gel was visualized with a UV transilluminator after running. The ACE gene I and D polymorphism genotypes were stated as II genotype single band 490 bp, ID genotype double band 190 bp and 490 bp, and DD genotype single band 190 bp, and profiling was performed (Figure 1).

### Statistical Analysis

For data analysis, IBM SPSS.23 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) was used. The chi-square test was used for categorical variables. Odds ratio values with 95% confidence intervals were given. The normal distribution for continuous variables

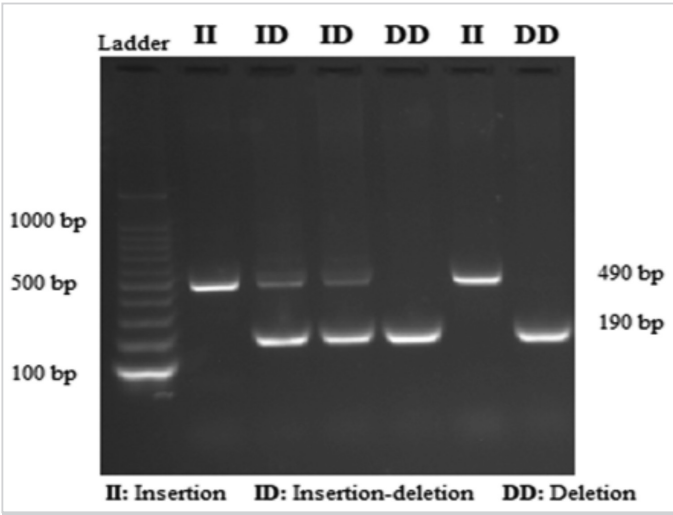


**Figure 1.** Gel electrophoresis of PCR-RFLP for blood samples in the ACE I/D polymorphism

PCR: Polymerase chain reaction, RFLP: Restriction fragment length polymorphism, ACE: Angiotensin-converting enzyme, I/D: Insertion/deletion

was checked with Shapiro Wilk's test of normality, and homogeneity of variance was controlled with Levene's test. Bi-level comparisons were made with the Mann-Whitney U test in patients where normal distribution was not present, and three-level comparisons were made with the Kruskal-Wallis H test. The statistical significance level was accepted as $p<0.05$.

## Results

The study group had a mean age of 46.50 (±13.69) years and consisted of 12 female (23.1%) and 40 male (76.9%) patients. In the control group, there were 25 female (18.0%) and 114 male (82.0%) patients, and their mean age was 46.8 (±15.63) years. No significant difference was stated between the groups regarding gender and age (p=0.428 and 0.888, respectively). Statistically significant differences were found between the study and control groups in genotype and allele distribution (p=0.015 and 0.003, respectively; Tables 1 and 2). In the study group, no significant differences were found in genotype distribution in terms of non-steroidal anti-inflammatory drug (NSAID) allergy, presence of asthma, and presence of NSAID-exacerbated respiratory disease (NERD) (p=0.645, 0.660, and 0.095, respectively; Table 3).

## Discussion

CRSwNP negatively affects patients' quality of life and reduces productivity at work. Despite the currently available medical, surgical, and combined treatments, it still has high recurrence rates (16). Systemic corticosteroids, which are effective agents in medical treatment, have the potential for serious side effects (17). Revision surgeries increase the risk of complications and the economic burden. Because of these difficulties in the treatment and control of the disease, studies are under way for the development of new treatment methods. CRS is a highly heterogeneous disease in terms of clinical presentation and pathophysiological mechanisms (18). In previous studies, it was suggested that T-helper (TH) 2 lymphocyte-mediated eosinophilic inflammation was mainly involved in the etiopathogenesis of CRSwNP; and TH1 lymphocyte-mediated neutrophilic inflammation was mainly associated with CRS without polyps (CRSsNP) (19). However, recent studies have shown that the inflammatory processes in the pathogenesis of CRS are more complex. Combined heterogeneous mechanisms involving TH1, TH2, TH17, and possibly TH22 lymphocytes have been identified (18). The key point in the development of CRSwNP is inflammation. Therefore, etiopathogenesis-based studies

**Table 1.** The study and control group comparison in terms of genotype and alleles

| | | Study Group | Control Group | p-value |
|---|---|---|---|---|
| | | n (%) | | |
| **Genotype** | II | 7 (13.5) | 41 (29.5) | 0.015 |
| | ID | 25 (48.1) | 69 (49.6) | |
| | DD | 20 (38.5) | 29 (20.9) | |
| **Allele** | I | 39 (37.5) | 151 (54.3) | 0.003 |
| | D | 65 (62.5) | 127 (45.7) | |

II: Insertion-insertion, I/D: Insertion/deletion, DD: Deletion-deletion

**Table 2.** Odds ratio values for ACE I/D gene polymorphism genotypes

| Genotype | OR | %95 Confidence interval | | p-value |
|---|---|---|---|---|
| | | Lower | Upper | |
| **II vs ID-DD** | 0.372 | 0.155 | 0.893 | **0.023** |
| **II vs ID-DD** | 0.939 | 0.497 | 1.777 | 0.847 |
| **DD vs II-ID** | 2.371 | 1.186 | 4.738 | **0.013** |

ACE: Angiotensin-converting enzyme, II: Insertion-insertion, I/D: Insertion/deletion, DD: Deletion-deletion

**Table 3.** Comparison of genotypes in terms of NSAID allergy, asthma, and NERD of the patients in the study group

| | | II n=7 | ID n=25 | DD n=20 | |
|---|---|---|---|---|---|
| | | n (%) | | | p-value |
| **NSAID allergy** | Yes | 5 (71.4) | 21 (84.0) | 15 (75.0) | 0.645 |
| | No | 2 (28.6) | 4 (16.0) | 5 (25.0) | |
| **Asthma** | Yes | 4 (57.1) | 16 (64.0) | 15 (75.0) | 0.660 |
| | No | 3 (42.9) | 9 (36.0) | 5 (25.0) | |
| **NERD** | Yes | 5 (71.4) | 24 (96.0) | 16 (80.0) | 0.095 |
| | No | 2 (28.6) | 1 (4.0) | 4 (20.0) | |

II: Insertion-insertion, I/D: Insertion/deletion, DD: Deletion-deletion, NERD: Non-steroidal exacerbated respiratory disease

aim to elucidate the mechanisms that trigger inflammation. In this study, we examined the I/D gene polymorphism of ACE, which was previously proven to be associated with inflammation, in patients with CRSwNP.

It has been shown that angiotensin II (a product of ACE) has a proinflammatory effect on leukocytes, endothelium, and vascular smooth muscle cells with its AT1 receptor (20-22). The pro-inflammatory effects of angiotensin II are largely mediated by increased oxidative stress and nuclear factor-kB. As a result of these mechanisms, proinflammatory cytokines like TNF-alpha, IL-1, and IL-6 are stimulated. Platelets also have angiotensin II receptors; angiotensin II binds to these receptors and releases mediators such as serotonin, norepinephrine, and histamine from the platelets (6). It is known that the cytokines and mediators mentioned above are involved in the etiopathogenesis of CRSwNP. Inflammatory pathways in which these cytokines and mediators participate support the results of our study. In our study, DD genotype and D allele were detected significantly more in CRSwNP cases than in the control group. ACE is higher in individuals with the D allele and this results in higher angiotensin II levels (7,8). Therefore, we believe that these patients may be more prone to chronic inflammation.

Recent studies have revealed that ACE II, which inactivates angiotensin II, is also highly expressed in the nasal mucosa (23). In a study by Fowler et al. (24) in which they compared CRSwNP patients and a healthy control group, it was determined that ACE II mRNA expression in non-polyp mucosal tissues was lower in CRSwNP patients. This result is supported by some previous studies (25,26). In the study of Wang et al. (25), a decrease in ACE II protein expression was observed in patients with CRSwNP and CRSsNP. A decrease in ACE II leads to an increase in angiotensin II. Therefore, the increase in these proinflammatory effects may be a predisposing factor in the formation of CRSwNP. In another study, IL-4, IL-5, and IL-13 levels (the main cytokines of TH2-mediated inflammation) were found to be higher in the nasal polyp tissue of CRSwNP patients with decreased ACE2 expression (26). According to these results, it is seen that angiotensin II increases indirectly in CRSwNP patients' tissues.

Similar results regarding ACE II mRNA expression were also found in studies about asthma and chronic rhinitis (27). In addition, Zhang et al. (13) meta-analysis of asthma and ACE I/D gene polymorphism found that the risk of asthma increased by 59% in patients with the DD genotype. We found no significant differences between the asthmatic cases in the study group and the patients without asthma in terms of genotype and alleles. This difference in our results may be related to the limited number of asthmatic patients in our study and/or ethnic differences. When we evaluated the study group patients in terms of NERD and NSAID allergy, we found no significant differences in terms of ACE I/D gene polymorphism. However, the number of cases also had to be limited to make these comparisons, so we think that these relationships should be evaluated in more comprehensive studies.

In addition to the strengths of our study, there are also some limitations. These include the exclusion of patient histories related to rhinitis subtypes, the lack of analysis of nasal mucosal inflammatory markers, the absence of classification and examination according to nasal polyp subtypes, the absence of the nasal polyp-nasal mucosa inflammatory markers and tissue ACE, and the limited number of patients for comparisons involving NERD, asthma and NSAID allergies.

## Conclusion

A statistically significant relationship between CRSwNP and ACE I/D gene polymorphism was found. This result suggests that ACE gene polymorphism may play a role in the development of CRSwNP. Future studies with larger sample sizes and different populations are needed to confirm these findings and to elucidate the mechanisms by which ACE polymorphisms influence CRSwNP.

### Ethics

**Ethics Committee Approval:** The research protocol of this study was approved by the Süleyman Demirel University Faculty of Medicine Clinical Research Ethics Committee Presidency (no: 240, date: 04.09.2020).

**Informed Consent:** Informed consent was taken from each patient.

### Footnotes

### Authorship Contributions

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

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

**Financial Disclosure:** This study was funded by The Coordinatorship of Scientific Research Projects Department (BAP), Süleyman Demirel University by the number of TSG-2020-8134.

**Main Points**

- The risk of chronic rhinosinusitis is higher in individuals with the deletion-deletion (DD) genotype and D allele of the angiotensin-converting enzyme (ACE) insertion/deletion gene polymorphism.
- The II genotype has the least risk of CRS with nasal polyps (CRSwNP).
- We think that this result is related to the high amount of ACE in patients with DD genotype.
- ACE and related pathways should be studied for the treatment of CRSwNP.

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# Long-term Prospective Comparative Analysis of Ototoxic and Survival Outcomes of Sequential Boost and Simultaneous Integrated Boost of Volumetric Modulated Arc Therapy for Head-Neck Carcinomas

Original Investigation

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## Abstract

**Objective:** To compare the ototoxicity and survival in head and neck carcinoma patients treated with sequential (SEQ) and simultaneous integrated boost (SIB) of volumetric modulated arc therapy (VMAT).

**Methods:** This long-term prospective study enrolled patients with histologically confirmed head and neck carcinoma, all receiving VMAT treatment. Audiological assessments were done using various tests at baseline, two weeks, treatment completion, six months, and 12 months. The changes in bone conduction pure tone thresholds were correlated with cochlear dose, comparing SEQ and SIB plans. We also investigated other significant late toxicities that led to dysphagia, voice changes, and xerostomia. Survival was assessed with the Kaplan-Meier analysis.

**Results:** The study included 93 patients (186 ears), 40 receiving radiation alone and 53 undergoing chemoradiation. Baseline hearing levels for the right and left ears were 13.3±2.3 dB and 14.2±1.5 dB. After 12 months of radiation, levels were 18.5±2.4 dB and 19.11±1.9 dB, respectively. No significant changes were observed between SEQ and SIB plans, but high-frequency shifts occurred. The cochlea tolerated up to 28 Gy without hearing loss in the radiation-alone group but showed loss at 9 Gy when combined with cisplatin chemotherapy. The maximum dose ($D_{max}$) and the mean dose ($D_{mean}$) of pharyngeal constrictor muscles predicted dysphagia. No significant SEQ vs. SIB differences were found in late toxicity or survival outcomes.

**Conclusion:** Modern radiotherapy techniques like VMAT adhere to cochlear dose limits. No significant differences were found between SEQ and SIB plans in sensorineural hearing loss, late toxicity, or survival, making both suitable for head and neck carcinoma treatment.

**Keywords:** Head and neck cancer, volumetric-modulated arc therapy, radiotherapy dose fractionation, ototoxicity, sensorineural hearing loss, survival analysis

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***Cite this article as:*** *Das N, Kombathula SH, Sharma V, Pareek P, Soni K, Goyal A. Long-term Prospective Comparative Analysis of Ototoxic and Survival Outcomes of Sequential Boost and Simultaneous Integrated Boost of Volumetric Modulated Arc Therapy for Head-Neck Carcinomas. Turk Arch Otorhinolaryngol. 2024; 62(3): 101-112*

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**Received Date:** 01-11-2023
**Accepted Date:** 10-01-2024

DOI: 10.4274/tao.2024.2023-10-10

## Introduction

According to 2020 data, cancer affects 6.46 million males, with head and neck malignancies ranking highest among men and fourth among women, primarily presenting in locally advanced stages in Asian countries like India (1,2). Radiotherapy (RT) plays a pivotal role in oncology treatment, but its drawback is the potential for acute and chronic organ toxicity (3). Innovations like intensity-modulated RT and volumetric arc therapy aim to mitigate this issue by focusing on the organs at risk (OAR) to spare them while delivering effective therapeutic doses (4).

Recent advancements in RT include novel techniques within volumetric modulated arc therapy (VMAT): Simultaneous integrated boost (SIB) plans and sequential plans (SEQ). SEQ involves administering radiation doses in distinct phases with identical fractions per phase. At the same time, SIB-IMRT (intensity-modulated radiotherapy) increases the dose to boost volume while maintaining a lower dose of the elective volume in the same fraction. SIB can shorten treatment duration and increases prescribed and biological doses. However, limited data exist on the response of normal tissues, tiny organs like the cochlea, to SIB/SEQ techniques (5-7).

This study aims to explore the ototoxic profile of SIB vs. SEQ VMAT plans in head and neck cancer patients undergoing RT. Secondary objectives include comparing the two plans' survival outcomes and other late toxicities. Given the novelty of this research, there is a lack of comprehensive data on the subject, particularly concerning sensorineural hearing loss (SNHL) and its progression post-radiation.

## Methods

In this prospective single-arm interventional study, we enrolled 93 individuals diagnosed with head and neck cancer who had no prior history of otological diseases after obtaining their informed consent. The study was conducted at All India Institute of Medical Sciences between January 2019 and December 2021. All India Institute of Medical Sciences, Jodhpur 3442005 (Raj.) Institutional Ethics Committe approval was obtained from the institution and the study was conducted within the scope of the specialization thesis of the first author (decision number: AIIMS/IEC/2019/1680, date: 21-01-2019).

All patients in the study received treatment at the Department of Otorhinolaryngology and Radiation Oncology. Exclusion criteria were age over 70 years, a history of or current otological disease, having previously undergone chemoradiation for head and neck conditions, and default on treatment.

The entire patient cohort was then grouped based on the primary disease subsite. The paranasal sinus region, nasopharynx, and parotid glands were classified as high-risk for cochlear irradiation, while all other major sites were classified as low risk.

It is worth noting that even though the cochlea is not intentionally included in the clinical target volumes (CTVs) for high neck and skull base malignancies, it does receive quantifiable dosages from the primary entrance, exit, and scattered beams, as illustrated in the dose-volume histograms.

### Radiotherapy

#### Simulation and Contouring

Patients were simulated using a 16-slice simulator (Optima 580, GE Healthcare, Waukesha, USA). Customized thermoplastic masks were made to immobilize the patients, and helical scans were performed with 1 mm slice thickness with intravenous contrast. Segmentation was undertaken in the Monaco planning system (V5.11.02 CMS Elekta, Sunnyvale, CA).

#### Segmentation and Treatment Planning

The gross tumor volume (GTV) encompasses all visibly diseased areas identified in the simulation computed tomography (CT) image. To create the high-risk CTV, we expanded the GTV by 5 mm. For the intermediate and low-risk CTVs, we adhered to the guidelines established by the radiation therapy oncology group (RTOG) (8).

It is important to note that the cochlea is particularly vulnerable when the retropharyngeal and retrostyloid nodes are subjected to radiation. For delineating cervical nodes, we followed the Trans-Tasman Radiation Oncology Group consensus guidelines (8). To establish the planning target volume (PTV), we applied a 3 mm margin around the CTV per institutional protocols. VMAT plans with a 6 mega volt beam were generated. Two arcs (in clockwise and anti-clockwise directions) were utilized in the plans with an increment angle of 20 degrees. A maximum of 180 control points with a segmental width of 1 cm were used for the plan optimization. Monte Carlo [(MC) v1.6)] algorithm was utilized using the cost functions of the contoured structures with a 3 mm grid size and 2% calculation uncertainty based on the performance of the VERSA HD linear accelerator (Elekta, UK). In the SEQ type of VMAT, the PTV receives a dose of 2 gray (Gy) per fraction during each phase. The accumulated prescribed doses for PTV-high, PTV-intermediate, and PTV-low in the SEQ approach are 66-70 Gy, 60 Gy, and 54-50 Gy, respectively. On the other hand, in the SIB type of VMAT, the prescribed dose to PTV-high, intermediate, and low are 66 Gy, 60 Gy, and 54 Gy all delivered in 30 fractions, respectively. It translates to a fractional dose of 2.2 Gy to PTV-high, 2 Gy to PT-intermediate, and 1.8 Gy to PT-low. Constraints were standardized according to the RTOG 0225 protocol.

The treatment was undertaken with image guidance on the first three consecutive days. If and if the shifts were within the limits of the PTV, an average shift was calculated and used for the rest of the treatments. After that, we used weekly cone beam computed tomography to confirm the accurate delivery of treatment.

**Cochlear Contouring and Dosimetry**

The cochlea possesses a conical structure with both an apex and a base and is positioned within the depths of the temporal bone, specifically within the otic capsule. The base of the cochlea is situated ventrally to the internal acoustic canal, while the apex is oriented in a ventrolateral and inferior direction towards the internal carotid artery. For this study, we followed the guidelines established by Sun et al. (9) to contour the cochlea. In our practical approach, we utilized a 1 mm CT slice with a bone window setting, adjusting the bone level to 1600 and the window width to 450 to accurately delineate the cochlea.

Patients were grouped as right/left/midline according to the primary disease site. In unilateral diseases, the cochlea on the same side as the primary disease site was given a higher dose of radiation compared to the cochlea on the opposite side. Accordingly, both cochleae were given similar doses in midline diseases like nasopharyngeal malignancy.

**Hearing Evaluation**

All patients underwent hearing evaluation before the initiation of treatment, at mid-treatment, at completion, at six months and 12 months. High-frequency pure tone audiometry (HFPTA), Impedance audiometry (Interacoustics, Denmark), and otoacoustic emission (OAE) (MAICO, Germany) were used to assess the auditory function at the above-mentioned time interval for all patients.

The HFPTA was performed using the MAICO-MA 42 clinical audiometer (MAICO, Germany). Bone conduction thresholds were obtained at 250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 hz frequencies.

**Hearing level/pure tone average:** Average of bone conduction sound thresholds at the following frequency in pure tone audiometer: 500, 1000, and 2000 hz.

**Significant hearing loss:** Defined as an increase in sound threshold in bone conduction average at 500,1000 and 2000 hz by more than 10 decibels (dB) from baseline reading.

**Frequency-specific hearing loss:** Increase in sound threshold by more than 10 dB in bone conduction at a specified frequency from baseline reading.

**Late toxicity:** Other significant late toxicities are dysphagia, change in voice, and xerostomia. The incidence of these symptoms was compared with the dose received [maximum dose within the target volume ($D_{max}$), mean dose within the target volume($D_{mean}$)] by the respective anatomical structures, that is, pharyngeal constrictor muscles, larynx, and parotid glands, respectively.

**Statistical Analysis**

Using median values, ranges, and frequencies, we employed statistical methods to represent patient, disease, and treatment characteristics. For dose-volume histograms, we calculated mean and median values for RT doses, cochlea volume, and cochlear doses (mean, minimum, and maximum) with standard deviations (SDs) and ranges. Right and left cochlear dosimetry was compared among laterality of disease using t test [expressed in t value, degree of freedom (df), p-value]. Repeated measure ANOVA compared hearing thresholds at different intervals, checking covariance equality with Box's test. Wilks' lambda test generated p-values in repeated measure ANOVA. Categorical data were compared using Pearson's chi-square test, and receiver operator characteristic (ROC) curves calculated predicted hearing loss doses. Qualitative data like tympanograms were assessed with the Mann-Whitney U test. Binary logistic regression determined dosimetric parameter odds ratios for late toxicity, and Kaplan-Meier analysis assessed cumulative hearing loss, overall survival (OS), disease-free survival (DFS), local control and regional control (RC), and progression-free survival (PFS), with log-rank tests. Cox proportional hazard models analyzed treatment outcomes. P-values <0.05 were considered significant. SPSS version 25 conducted all statistical tests.

## Results

**Patient Demography and Clinical Features**

The median age was 54 (range: 28-76). The major site of presentation was the oral cavity, and the most common stage of presentation was stage IVa. Other results are detailed in Table 1.

**Dosimetry**

The dosimetric comparison for both target and OAR is tabulated in Table 2. The dosimetric parameters in the target were comparatively higher in SEQ plans, but the difference was not statistically significant. The dosimetric characteristics of both SEQ and SIB plans were within the guidelines by quantitative analyses of normal tissue effects in the clinic (QUANTEC). There was no statistically significant difference in the OAR constraints between the two plans.

**Cochlear Dosimetry and Hearing Loss**

Out of the 40 patients who received RT alone as a treatment, 21 underwent the SEQ plan, and 19 underwent the SIB plan

**Table 1.** Clinical features and demography

| Variables | Number | Percentage (%) |
|---|---|---|
| Age: median (range) years | 54 (28-76) | |
| **Gender** | | |
| Male | 75 | 80.6% |
| Female | 18 | 19.4% |
| **Primary site** | | |
| Oral cavity | 42 | 45.16% |
| Oropharynx | 18 | 19.35% |
| Hypopharynx | 7 | 7.52% |
| Larynx | 15 | 16.12% |
| Nasopharynx | 3 | 3.22% |
| Nose and PNS | 4 | 4.30% |
| Salivary glands | 4 | 4.30% |
| **T stage** | | |
| $T_1$ | 9 | 9.67% |
| $T_2$ | 16 | 17.20% |
| $T_3$ | 17 | 18.27% |
| $T_4$ | 51 | 54.83% |
| **N stage** | | |
| $N_0$ | 8 | 8.60% |
| $N_1$ | 19 | 20.43% |
| $N_2$ | 49 | 52.68% |
| $N_3$ | 17 | 18.27% |
| **Prognostic stage** | | |
| I | 9 | 9.67% |
| II | 16 | 17.20% |
| III | 17 | 18.27% |
| IVA | 42 | 45.16% |
| IVB | 9 | 9.67% |
| **Treatment** | | |
| RT alone | 40 | 43.1% |
| Chemoradiation | 53 | 56.9% |
| **Type of RT** | | |
| Adjuvant RT | 49 | 52.6% |
| Definitive RT | 44 | 47.4% |
| **Plan** | | |
| SEQ-VMAT | 56 | 60.3% |
| SIB-VMAT | 37 | 39.7% |

RT: Radiotherapy, SEQ-VMAT: Sequential volumetric modulated arc therapy, SIB: VMAT: Simultaneous integrated boost-Volumetric modulated arc therapy, PNS: Paranasal sinus

VMAT. Statistical analysis of hearing loss for 53 patients who received chemoradiation was performed separately to avoid bias, as cisplatin is already a proven ototoxic drug.

The entire cohort was grouped as right, left, and midline according to the laterality of the primary disease site. The mean doses received by both cochleae were compared and found to be statistically different from each other in right and left-sided diseases, with the ipsilateral cochlea receiving higher doses (Right: p-0.02, df-21, t 3.1) (Left: p-0.04, df-15, t-1.8) (Midline: p-0.76, df-4, t-1.26). The mean dose reaching the cochlea was 8.5±7.8 Gy (right 8.2±7.1 Gy and left 7.9±6.8 Gy).

The mean baseline (n=40) hearing level on the right side was 13.3±2.3 dB, and that of the left was 14.2±1.5 dB. After 12 months of RT, the mean hearing level on the right side was 18.5±2.4 dB, and the left was 19.11±1.9 dB. There was no statistically significant difference along the study's bone conduction pure tone average timeline. There was no statistically significant difference in pure tone average between both plans (Box's M-20.12, F-31.62, $df_1$-8, $df_2$-1102.3, p=0.0021) (Wilks' Lambda- 0.312, F-21.63, p=0.003) (Table 3).

On analysis of change in frequency-specific hearing thresholds, we found a statistically significant difference at high frequency (4Khz-8Khz) hearing thresholds from baseline reading to 12 months of RT completion (Wilks' Lambda-0.366, F-31.23, p=0.04) in both RT plans (Appendix Table 1). All the threshold shifts observed at bone conduction indicate SNHL. The threshold shift was progressive until the 12$^{th}$ month of the study and was started predominantly at 6 months. However, there was no statistically significant difference between SEQ-VMAT and SIB-VMAT plans at any frequency at any specified study time (Figure 1).

Fifty-three individuals underwent concurrent cisplatin-based chemotherapy in this study. Among these participants, 49 individuals were administered weekly cisplatin concurrently, with an average dosage of 60 mg (ranging from 25 to 45 mg/m$^2$) over a median of three cycles (ranging from 1 to 5 cycles). Additionally, four patients received a single 250 mg dose of paclitaxel in combination with cisplatin as part of their induction chemotherapy.

In the chemoradiation arm, ROC curves were used at each auditory frequency to calculate the minimum dose at which hearing loss occurred when combined with chemoradiation. The results of patients who received radiation alone revealed that the cochlea received maximum doses of up to 28.52 Gy without causing SNHL. But along with chemotherapy (cisplatin), hearing loss occurred at a minimum dose of 9 Gy. The minimum dose cut to predict hearing loss is given in Table 4. Further, we compared the cumulative hearing loss between both plans using the Kaplan-Meier plot. The censorship was kept as the occurrence of hearing loss, and the end of follow-up was kept at 12 months. There was no statistically significant difference between both plans by log-rank test (chi-square- 33, df- 2, p=0.98).

**Table 2.** Dosimetric characteristics of VMAT

| Variables | Parameters | QUANTEC dose-volume constraints for organs-at-risk | SEQ-VMAT | SIB-VMAT | p-value |
|---|---|---|---|---|---|
| **Target** | | | | | |
| PTV high risk | $D_{mean}$ (Gy) | | 68.5 (68.4 - 69.3) | 69.5 (67.5 - 68.4) | 0.89 |
| | V95 (%) | >95 | 98.0 (97.1 - 99.9) | 99.1 (98.2 - 99.9) | 0.76 |
| | V107 (%) | <1 | 0.50 (0.00 - 3.10) | 0.5 (0.00 - 3.1) | 0.45 |
| | D98% (Gy) | >60.8 | 63.1 (62.0 - 64.2) | 64.1 (62.3 - 66.5) | 0.32 |
| | HI | | 11.8 (7.6 - 14.3) | 12.1 (7.2 - 14.5) | 0.56 |
| | CI1 | | 1.73 (1.62 - 3.12) | 1.91 (1.62 - 3.02) | 0.21 |
| | % DCI1-2 | | 97.6 (94.9 - 99.2) | 98.1 (93.9 - 99.7) | 0.08 |
| | % DCI1-3 | | 95.5 (94.9 - 97.4) | 96.1 (95.1 - 97.1) | 0.33 |
| PTV intermediate risk | V95 (%) | >95 | 98.9 (97.8 - 99.9) | 99.1 (98.8 - 99.9) | 0.06 |
| | D98 % (Gy) | >57 | 58.3 (56.7 - 60.3) | 58.9 (57.7 - 60.4) | 0.07 |
| | CI2 | | 1.79 (1.63 - 2.51) | 1.84 (1.61 - 2.93) | 0.09 |
| PTV LR | V95 (%) | >95 | 98.9 (98.0 - 99.7) | 99.1 (98.1 - 99.8) | 0.65 |
| | D98 % (Gy) | >50 Gy | 53.8 (52.6 - 55.0) | 54.1 (52.8 - 55.9) | 0.76 |
| | CI3 | | 1.55 (1.49 - 1.81) | 1.61 (1.50 - 1.91) | 0.09 |
| **Organ at risk** | | | | | |
| Cochlea | $D_{mean}$ (Gy) | <45 Gy | 8.5 (8.1-9.2) | 9 (8.2-10.5) | 0.42 |
| | $D_{max}$ (Gy) | | 9.29 (8.3-10.5) | 10.3 (9.1-11.2) | 0.16 |
| Larynx | $D_{mean}$ (Gy) | <44 Gy | 44.41 (43.6-46.3) | 44.8 (43.8-45.9) | 0.21 |
| Right parotid gland | $D_{mean}$ (Gy) | <26 Gy | 23.8 (22.6-25.2) | 24.76 (23.7-26.3) | 0.08 |
| Left parotid gland | $D_{mean}$ (Gy) | <26 Gy | 24.3 (23.1-26.8) | 24.8 (21.6-25.5) | 0.33 |
| Pharyngeal constrictors | $D_{mean}$ (Gy) | | 52.1 (49.2-55.6) | 53.2 (49.1-54.3) | 0.86 |
| Lenses | $D_{mean}$ (Gy) | <55 Gy | 1.3 (1.2-4.8) | 1.5 (1.1-4.5) | 0.27 |
| Brain stem | D1, cc (Gy) | <54 Gy | 31.2 (26.0-37.7) | 32.2 (26.9-38.7) | 0.33 |
| | EUD (Gy) | | 23.8 (18.9-24.8) | 24.1 (19.9-25.5) | 0.06 |
| | NTCP (%) | | 0.0 (0.0-0.0) | 0.0 (0.0-0.0) | 0.17 |
| Spinal cord | D1, cc (Gy) | <45 Gy | 36.9 (35.8 - 43.8) | 36.4 (35.2 - 44.9) | 0.09 |
| | EUD (Gy) | | 31.8 (24.9 - 33.5) | 31.1 (25.9 - 34.5) | 0.65 |
| | NTCP (%) | | 0.0 (0.0 - 0.0) | 0.0 (0.0 - 0.0) | 0.77 |
| Optic nerve | $D_{mean}$ (Gy) | | 2.8 (1.8 - 14.3) | 3.1 (1.9 - 14.9) | 0.09 |
| | $D_{max}$ (Gy) | <55 Gy | 4.2 (1.4 - 28.9) | 4.9 (1.9 - 29.2) | 0.98 |

HI: Homogeneous index, CI: Conformity index, EUD: Equivalent uniform dose, NTCP: Normal tissue complication probability, SEQ-VMAT: Sequential volumetric modulated arc therapy, PTV: Planning target volume, SIB-VMAT: Simultaneous integrated boost volumetric modulated arc therapy, QUANTEC: Quantitative analyses of normal tissue effects in the clinic, $D_{max}$: Maximum dose within the target volume, $D_{mean}$: Mean dose within the target volume

Impedance audiometry was analyzed in two domains: compliance and type of graph. 5.6% of the ears exhibited a change in tympanogram (A to B) during treatment, indicative of otitis media, which resolved in 4.1% of ears six months after therapy was completed. There was no statistically significant difference between the SEQ-VMAT and SIB-VMAT plans in impedance parameters.

OAEs were compared between time intervals, and there were no statistically significant differences between baseline and 12 months OAE reading by repeated measure ANOVA (Wilks' Lambda- 0.43, F- 32.13, p=0.86). Similarly, OAE were compared between SEQ-VMAT and SIB-VMAT, and there was no statistically significant difference between the two at the end of the 12- month follow-up in both TOAE (t- 2.81, df- 40, p=0.89) and DPOAE (t- 2.76, df- 40, p=0.43).

### Late Toxicities

The dosimetry of parotid glands, pharyngeal constrictor muscles, and larynx were analyzed further to define the dose constraints for late toxicity. There was no statistically

**Table 3.** Distributions of median (range) hearing thresholds in various frequencies and the results of ANOVA

| Frequency | Baseline | | Mid-fraction (2 weeks) | | Completion | | 6 months | | 12 months | | p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Right | Left | Right | Left | Right | Left | Right | Left | Right | Left | |
| Hearing level (Average of 500,1 Khz, and 2 Khz) | 13.1 (11.2-15.2) | 13 (11.7-14.4) | 13.33 (11.7-14.9) | 13.8 (11.2-14.2) | 14.8 (13.1-16.2) | 14 (13.9-17.1) | 16.62 (15.7-18.9) | 16 (15-17.3) | 19.87 (18.9-21.1) | 20.07 (19.1-22.2) | 0.45 |
| 250 | 10.1 (8.9-11.2) | 11 (9.2-12.3) | 10.1 (9.2-12.1) | 9.1 (8.9-11.2) | 11.2 (10.3-12.7) | 12.1 (10.3-12.7) | 13.8 (11.9-15.3) | 13.33 (11.01-14.9) | 15.1 (14.2-16.8) | 16.6 (15.1-17.8) | 0.89 |
| 500 | 15.2 (12.1-16.4) | 14.9 (13.2-16.4) | 15.29 (13.2-16.5) | 14.2 (12.1-16.4) | 15.5 (14.2-17.3) | 14.9 (13.9-17.3) | 17.2 (15.5-18.8) | 17.1 (16.5-18.56) | 19.3 (18.2-20.3) | 18.9 (17.2-21.3) | 0.76 |
| 1000 | 13.5 (11.2-15.2) | 12.5 (11.7-13.9) | 13.5 (11.7-14.9) | 13.3 (11.2-15.2) | 14.8 (13.8-16.2) | 14 (13.3-17.2) | 17.97 (15.7-18.9) | 17.71 (16.6-19.9) | 20.1 (18.9-21.1) | 20 (18.2-22.1) | 0.23 |
| 2000 | 10.3 (8.3-12.2) | 11.1 (8.9-11.9) | 10.3 (8.9-11.8) | 11.1 (8.3-12.2) | 14.1 (13.3-15.9) | 14.1 (12.9-15.8) | 15.7 (13.4-16.3) | 15.5 (14.4-17.3) | 20.2 (19.3-21.4) | 21.1 (19.9-22.4) | 0.04 |
| 4000 | 15.3 (13.4-16.4) | 14.3 (13.6-15.8) | 15.3 (13.6-16.8) | 13.1 (13.4-16.4) | 21.2 (18-22.9) | 20.2 (19.1-21.9) | 31.3 (29.7-32.5) | 30.3 (28.8-33.3) | 38.2 (37.2-39.9) | 39.2 (37.2-40.9) | 0.02 |
| 8000 | 15.6 (13.8-17.3) | 14.6 (14.1-16.2) | 15.6 (14.1-17.2) | 16.1 (14.8-17.3) | 23 (21.2-24.9) | 22.2 (21.1-24.7) | 34.8 (31.7-35.8) | 35.8 (32.1-36.3) | 41.1 (39.6-42.5) | 41.1 (40.6-42.5) | <0.001 |




**Figure 1.** Kaplan-Meier plot for cumulative hearing loss showing the comparison of SEQ vs. SIB plans with p-value generated by log-rank test

SEQ: Sequential, SIB: Simultaneous integrated boost

**Table 4.** ROC curve values of predicted RT dose causing hearing loss

| Frequency (bone conduction) hz | 500 hz | 1000 hz | 2000 hz | 4000 hz | 8000 hz |
|---|---|---|---|---|---|
| Mean dose cut-off by youden's index method (Gy) | 6.34 | 22.2 | 4.9 | 7.99 | 11.91 |
| Area under | 0.64 | 0.621 | 0.69 | 0.66 | 0.61 |
| Sensitivity | 63.5 | 40 | 77.8 | 55.8 | 46.8 |
| Specificity | 61.1 | 90.4 | 54.6 | 75.4 | 80.3 |
| p-value | 0.02 | 0.001 | 0 | 0.001 | 0.01 |

ROC: Receiver operator characteristic, RT: Radiotherapy, Gy: Gray

**Table 5.** Binary logistic regression to assess the risk of developing late toxicity as a function of dose received by the target volume

| Binary logistic regression | Parameter (Gy) | Odd's ratio (95% CI) | p-value |
|---|---|---|---|
| Constrictor muscles of pharynx | $D_{max}$ | 1.41 (0.98-2.12) | 0.021 |
| | $D_{mean}$ | 1.23 (0.21-3.12) | <0.001 |
| Larynx | $D_{max}$ | 0.98 (0.11-2.32) | 0.86 |
| | $D_{mean}$ | 0.76 (0.18-1.99) | 0.45 |
| Right parotid | $D_{max}$ | 1.09 (0.23-2.82) | 0.09 |
| | $D_{mean}$ | 1.04 (0.71-2.31) | 0.33 |
| Left parotid | $D_{max}$ | 1.12 (0.89-3.21) | 0.24 |
| | $D_{mean}$ | 0.99 (0.31-1.98) | 1 |

$D_{max}$: Maximum dose within the target volume, $D_{mean}$: Mean dose within the target volume, Gy: Gray, CI: Confidence interval

significant difference between SIB vs. SEQ plans in patients who developed dysphagia (42.3% vs. 40.7%), change in voice (9.4% vs. 8.9%), and xerostomia (51.4% vs. 53.3%). On binary logistic regression, the $D_{max}$ and $D_{mean}$ of pharyngeal constrictor muscles were predictors for dysphagia with statistically significant results (Table 5). The odds ratio for developing dysphagia was 1.4 when $D_{max}$ was above 50 Gy. There was no statistically significant difference between SEQ and SIB VMAT plans in the incidence of late toxicity.

### Survival Analysis

The mean follow-up time was 13.5±1.2 (mean±SD) months. The mean survival time was 723.2±1.6 days (mean±standard error) (95% CI: 710.76-765.6). The OS was 63.8% at the end of 12 months. There was no statistically significant difference between SEQ and SIB in OS (62.8% vs. 60.9%, p=0.89), DFS (62.1% vs. 52.4%, p=0.67), LC (58.7% vs. 57.6%, p=0.57), RC (95.2% vs. 89.3%, p=0.25) and PFS (72.1% vs. 69.2%, p=0.87) (Figure 2). Univariate and multivariate Cox hazard model analysis for the treatment plan is given in Table 6. The subgroup analysis of two-year survival in the RT and chemoradiation groups according to the primary site is given in Appendix Table 2.

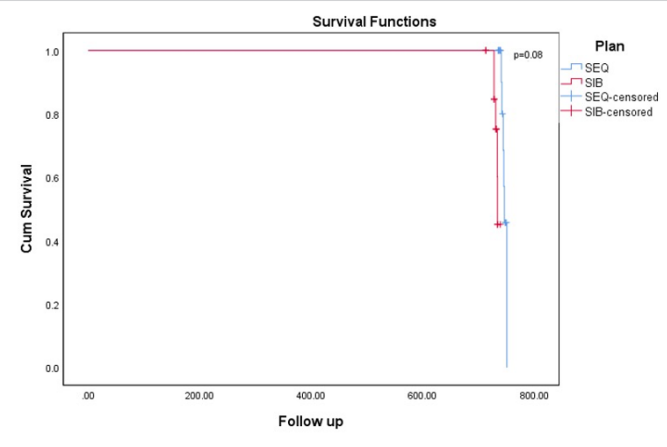


**Figure 2.** Kaplan-Meier plot for cumulative survival showing the comparison of survival between SEQ vs. SIB. P-value generated by log-rank test

SEQ: Sequential, SIB: Simultaneous integrated boost

## Discussion

Advancements in dosimetry accuracy and the need for shorter treatments drive the adoption of novel delivery techniques. Transitioning from 2D RT to IMRT has reduced treatment toxicity, leading to the adoption of advanced methods like VMAT. SIB/SEQ is now the standard for complex malignancies. Research on toxicity profiles is ongoing, including ototoxicity (5,10-13). In head and neck radiation therapy (RT), precise target dose determination is crucial for effective treatment with minimal side effects. Factors like tumor characteristics, patient-related factors, and potential tissue toxicity must be considered. The study of Morgan and Sher (14) emphasizes the roles of tumor size, location, and stage. Proximity to critical organs like the lenses, the spinal cord, and the salivary glands is vital. Patient health, comorbidities, and prior treatments also impact the dose. Balancing tumor control and tissue preservation enhances outcomes and quality of life for head and neck cancer patients (15).

In this study, the SEQ-VMAT and SIB-VMAT treatment techniques met the prescribed dose requirements for target volumes and effectively spared OAR. While there was no significant difference in achieved dose coverage to the target between the two techniques, the homogeneity index was notably lower in SEQ-VMAT for PTV-intermediate and PTV-low. The SIB-VMAT approach, with its high prescription dose to $PTV_1$ and attachment of $PTV_2$ and $PTV_3$, led to higher dose inhomogeneity in nearby target regions. SEQ-VMAT resulted in more uniform doses to the target structures. Furthermore, patients treated with SIB-VMAT showed lower doses to the pharyngeal constrictors and brainstem, indicating that the SIB technique is advantageous in delivering lower doses to critical structures. However, these findings were statistically not significant. Kachhwaha et al. (16) conducted a prospective comparison of SEQ versus SIB of VMAT in treating 54 oropharyngeal carcinoma patients. Their results were like the presented study.

According to QUANTEC guidelines (17), the recommended safe mean dose constraint for the cochlea is <45 Gy. Our

**Table 6.** Treatment outcomes, Cox proportional hazard model

| Treatment outcomes | Univariable | | Multivariable | |
|---|---|---|---|---|
| | SEQ vs. SIB [hazard ratio (95% CI)] | p-value | SEQ vs. SIB [hazard ratio (95% CI)] | p-value |
| OS | 0.56 (0.32–2.25) | 0.87 | 1.24 (0.24-2.31) | 0.76 |
| DFS | 0.57 (0.29-1.52) | 0.23 | 0.65 (0.33-1.49) | 0.21 |
| LC | 0.68 (0.42-1.89) | 1.01 | 0.70 (0.27-1.62) | 0.43 |
| RC | 0.35 (0.24-1.78) | 0.22 | 0.14 (0.02–2.78) | 0.55 |
| PFS | 0.42 (0.31-2.13) | 0.43 | 0.12 (0.01-1.13) | 0.08 |

OS: Overall survival, DFS: Disease-free survival, LC: Local control, RC: Regional control, PFS: Progression-free survival, SEQ: Sequential, SIB: Simultaneous integrated boost, CI: Confidence interval

study successfully adhered to this constraint. Lamaj et al. (18) investigated hearing impairment in nasopharyngeal carcinoma patients undergoing chemoradiotherapy (CRT). They aimed to spare the cochlea while using IMRT and VMAT to maintain treatment effectiveness. Re-optimized plans significantly reduced cochlear dose ($p<0.001$) without compromising other quality parameters. Their study demonstrates the feasibility of preserving cochlear function in nasopharyngeal carcinoma patients during CRT. It underscores the importance of considering hearing toxicity in treatment planning due to the absence of a defined dose threshold for CRT-induced hearing impairment.

In a retrospective study by Vlacich et al. (19), researchers conducted a matched cohort analysis on locally advanced head and neck carcinoma patients treated with chemoradiation. A total dose of 69.3 Gy in 33 fractions was administered to 209 patients, 68 receiving SEQ and 141 receiving SIB treatment. Results revealed no significant differences in DFS (63% vs. 69%; p=0.27) and OS (69.3% vs. 76.8%; p=0.13) between the SEQ and SIB groups. However, the SIB group exhibited a higher incidence of grade 3 or 4 acute dysphagia (82% vs. 55%) and acute dermatitis (78% vs. 58%). Interestingly, our study showed no difference in grade 3 dysphagia incidence between the SEQ (11.5%) and SIB (19.2%) groups (p=0.44). The dissimilarity in patient populations may explain this, as Vlacich et al.'s (19) study included oropharyngeal cancer patients, potentially accentuating differences in SIB vs. SEQ techniques due to retropharyngeal node involvement.

Our study, involving 40 head and neck cancer patients treated with RT alone, examined the impact on hearing. We focused on definitive or adjuvant RT without chemotherapy. Our model suggested that the cochlea could tolerate doses up to 28.52 Gy without causing SNHL in this context, with exceptions at 4 Khz and 8 Khz frequencies in the RT-only group. We conducted further investigations and referenced the relevant literature. Regarding treatment plans, there were no statistically significant differences between SEQ and SIB plans, aligning with Pan et al.'s (20) study on 3D CRT planning. Our study found a lower median cochlear dose at 4.2 Gy (range: 0.38 to 56.6 Gy) irrespective of the disease side, with consistent cochlear volume exposure (0.56 $cm^3$ vs. 0.14 $cm^3$) compared to Pan et al. (20). All patients underwent VMAT treatment, ensuring adherence to safe cochlear dose constraints and potentially reducing the risk of immediate SNHL post-RT.

Apart from audiometry, otoacoustic emissions, measured at different intervals, did not significantly differ from baseline or between treatment plans. In a prospective study, Akazawa et al. (21) explored RTs impact on the Eustachian tube and middle ear functions in head and neck cancer patients. They identified Eustachian tube dysfunction as a common complication. Our study examined 186 ears and found a 5.6% change from curve type A to B, mainly on the right side, associated with reduced right tympanic membrane compliance (p=0.029), often occurring mid-treatment. However, 73% of the affected ears recovered within six months. Considering the disease laterality, the skewed data suggests a potential statistical artifact. In summary, radiation-induced middle ear dysfunction may contribute significantly to conductive hearing loss.

Our research revealed no hearing impairment in patients solely treated with VMAT RT. However, when combined with cisplatin, the clinically significant high-frequency hearing loss occurred at an average cochlear RT dose of approximately 9 Gy. Hitchcock et al.'s (22) prospective study involving 62 head and neck cancer patients investigated dose-related hearing loss in patients receiving RT, cisplatin, or both. For RT alone, no significant hearing loss was seen below 40 Gy. In patients receiving cisplatin, even lower radiation doses (10 Gy) led to hearing loss at 8000 hz, worsening with higher doses (40 Gy).

In a randomized phase III study comparing SEQ and SIB intensity-modulated RT for nasopharyngeal carcinoma, grade 3-5 mucositis, and dysphagia were the most common acute toxicities. However, no statistically significant differences were found in the cumulative incidence of grade 3-4 acute toxicities between the two treatment approaches (SEQ and SIB). Late toxicities included hearing loss, temporal lobe injury, cranial nerve injury, and xerostomia, consistent with our findings. Pharyngeal constrictor muscle $D_{max}$ and $D_{mean}$ were predictors for dysphagia (odds ratio 1.4 for $D_{max}$>50 Gy). Three-year PFS and OS rates showed no significant differences between SEQ and SIB (p=0.488 and p=0.938, respectively) during the 41-month median follow-up (23).

Shivananjappa et al. (24) shared their experience using SIB VMAT (SIB VMAT) to treat head and neck cancer definitively. Their prospective randomized study included 50 patients with stage T1-3 squamous cell carcinoma of the oropharynx, hypopharynx, and larynx, with enlarged nodes ≤3 cm. Patients were split into hypo-fractionated SIB (Hypo-SIB VMAT) and conventional boost VMAT (Conv-VMAT). After two years, OS rates were 84% (Hypo-SIB VMAT) and 80% (Conv-VMAT), with no significant differences (p=0.25). DFS was 88% vs. 72% (p=0.12), and locoregional recurrence-free survival (RFS) was 92% vs. 84% (p=0.38). Both arms had similar toxicities, but Hypo-SIB VMAT had a significantly shorter average overall treatment time (39.4 vs. 50.2 days, p=0.00001).

## Conclusion

In conclusion, both SEQ and SIB plans met the QUANTEC guidelines with similar dosimetric characteristics, showing no significant differences in target and organ-at-risk constraints. The RT-alone group had

no significant hearing loss, with the cochlea tolerating up to 28 Gy without issues. However, when combined with cisplatin-based chemotherapy, frequency-specific hearing loss emerged at 9 Gy, especially in high frequencies (4 Khz-8 Khz). These findings suggest the importance of stricter cochlear dose constraints when using cisplatin and RT. Late toxicities, specifically dysphagia, were correlated with higher pharyngeal constrictor muscle $D_{max}$ and $D_{mean}$. Survival outcomes did not significantly differ between the two treatment plans.

### Ethics

**Ethics Committee Approval:** The study was conducted at All India Institute of Medical Sciences between January 2019 and December 2021. Ethics and research committee approval was obtained from the institution and the study was conducted within the scope of the specialization thesis of the first author (decision number: AIIMS/IEC/2019/1680, date: 21-01-2019).

**Informed Consent:** In this prospective single-arm interventional study, we enrolled 93 individuals diagnosed with head and neck cancer who had no prior history of otological diseases after obtaining their informed consent.

### Footnotes

### Authorship Contributions

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

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

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

### Main Points

- In this study, we evaluated the effectiveness of modern-day radiotherapy techniques in sparing the organ at risk in the context of early & late radiation toxicity and survival in head and neck cancer patients.
- The cochlea exhibited varying radiation tolerance levels. In the radiation-only group, the cochlea demonstrated tolerance up to 28 Gy without the incidence of hearing loss. However, hearing loss was observed at a minimum of 9 Gy in the chemoradiation group.
- There was no significant difference in ototoxicity between sequential (SEQ) and simultaneous integrated boost plans of volumetric modulated arc therapy.
- The maximum dose ($D_{max}$) and the mean dose ($D_{mean}$) received by pharyngeal constrictor muscles can predict late toxicity, such as dysphagia.
- Notably, there were no significant differences in late toxicity or survival outcomes between the SEQ and simultaneous integrated boost plans of volumetric modulated arc therapy.

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**Appendix Table 1.** Comparison of hearing thresholds among SEQ & SIB across different time interval of the study

| Hearing Frequency (hz) | Baseline thresholds (dB) | | | Mid-fraction Thresholds (dB) | | | Completion thresholds (dB) | | | 6 months thresholds (dB) | | | 12 months thresholds (dB) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | SEQ-VMAT | SIB-VMAT | p-value | SEQ-VMAT | SIB-VMAT | p-value | SEQ-VMAT | SIB-VMAT | p-value | SEQ-VMAT | SIB-VMAT | p-value | SEQ-VMAT | SIB-VMAT | p-value |
| 250 | 10.1 (8.9-11.2) | 10 (8.2-11.4) | 0.98 | 10.1 (9.2-12.1) | 10 (9.1-11.7) | 0.18 | 11.2 (10.3-12.7) | 11 (10.5-13.1) | 0.68 | 13.9 (11.1-14.2) | 13.8 (11.9-15.3) | 0.72 | 15.1 (14.2-16.8) | 14.3 (12.3-15.6) | 0.84 |
| 500 | 15.2 (12.1-16.4) | 15.1 (13.1-16.8) | 0.06 | 15.29 (13.2-16.5) | 15.1 (14.2-16.9) | 0.36 | 15.5 (14.2-17.3) | 15.4 (14.2-16.9) | 0.24 | 17.3 (15.3-19.3) | 17.2 (15.5-18.8) | 0.37 | 19.3 (18.2-20.3) | 18.6 (17.3-19.3) | 0.56 |
| 1000 | 13.5 (11.2-15.2) | 13.4 (11.6-15.4) | 0.45 | 13.5 (11.7-14.9) | 13.4 (12.1-15.3) | 0.25 | 14.8 (13.8-16-2) | 14.57 (13.1-16.7) | 0.45 | 18.2 (17.2-20.1) | 17.97 (15.7-18.9) | 0.45 | 20.1 (18.9-21.1) | 19.85 (18.4-21.5) | 0.66 |
| 2000 | 10.3 (8.3-12.2) | 10.2 (9.3-12.1) | 0.54 | 10.3 (8.9-11.8) | 10.2 (7.9-12.1) | 0.14 | 14.1 (13.3-15.9) | 13.8 (12.1-14.5) | 0.65 | 14.9 (12.9-16.7) | 14.7 (13.4-15.3) | 0.44 | 20.2 (19.3-21.4) | 20.1 (18.9-21.1) | 0.73 |
| 4000 | 15.3 (13.4-16.4) | 15.2 (13.6-16.1) | 0.22 | 15.3 (13.6-16.8) | 15.2 (12.9-14.6) | 0.42 | 21.2 (18-22.9) | 21.08 (19.9-22.3) | 0.99 | 32.2 (30.4-33.3) | 31.3 (29.7-32.5) | 0.12 | 38.2 (37.2-39.9) | 37.33 (36.2-38.1) | 0.37 |
| 8000 | 15.6 (13.8-17.3) | 15.5 (12.9-16.8) | 0.21 | 15.6 (14.1-17.2) | 15.2 (12.9-14.6) | 0.61 | 23 (21.2-24.9) | 22.8 (20.2-23.9) | 0.09 | 35 (30.5-37.5) | 34.8 (31.7-35.8) | 0.81 | 41.1 (39.6-42.5) | 41 (38.8-42.1) | 0.21 |

SEQ: Sequential, SIB: Simultaneous integrated boost, VMAT: Volumetric modulated arc therapy

**Appendix Table 2.** Subgroup analysis of 2-year survival

| Primary site | RT alone | | Chemoradiation | | p-value |
|---|---|---|---|---|---|
| | 2-year survival (%) | p-value | 2-year survival (%) | p-value | (RT vs. Chemo RT) |
| **Oral cavity** | | | | | |
| SIB | 81 | 0.65 | 85 | 0.55 | 0.99 |
| SEQ | 79 | | 81 | | |
| **Oropharynx** | | | | | 0.06 |
| SIB | 72 | 0.99 | 79 | 0.19 | |
| SEQ | 75 | | 74 | | |
| **Larynx** | | | | | 0.11 |
| SIB | 69 | 0.07 | 72 | 0.57 | |
| SEQ | 72 | | 73 | | |
| **Hypopharynx** | | | | | 0.29 |
| SIB | 79 | 0.06 | 76 | 0.34 | |
| SEQ | 81 | | 74 | | |
| **Nose and paranasal sinuses** | | | | | 0.08 |
| SIB | 71 | 0.23 | 77 | 0.09 | |
| SEQ | 69 | | 74 | | |
| **Nasopharynx** | | | | | 0.77 |
| SIB | 90 | 0.09 | 91 | 0.44 | |
| SEQ | 88 | | 90 | | |
| **Salivary glands** | | | | | 0.31 |
| SIB | 98 | 0.98 | 89 | 0.78 | |
| SEQ | 96 | | 90 | | |

SEQ: Sequential, SIB: Simultaneous integrated boost, RT: Radiotherapy

# Comparative Analysis of Preoperative Sedation Modalities: Oral Midazolam and Ketamine Versus Chloral Hydrate and Meperidine in Pediatric Tonsillectomy - A Randomized Clinical Trial

Original Investigation

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## Abstract

**Objective:** A pre-anesthetic medication that is ideal for pediatric patients undergoing tonsillectomy should alleviate pediatric anxiety, facilitate the smooth induction of anesthesia, and have an analgesic effect for postoperative care. This study compared the effectiveness of an oral combination of midazolam and ketamine (MK) with an oral combination of chloral hydrate and meperidine (CM) as premedication in pediatric patients undergoing tonsillectomy.

**Methods:** This double-blind clinical trial study was conducted with 68 pediatric patients scheduled to undergo tonsillectomy. The participants were randomly allocated into two groups: the CM group, which received oral premedication of 50 mg/kg chloral hydrate and 1.5 mg/kg meperidine, and the MK mixture group, which received oral premedication of 0.5 mg/kg midazolam and 5 mg/kg ketamine. Various parameters such as separation anxiety, agitation during emergence from anesthesia, postoperative pain, postoperative nausea, and vomiting, as well as respiratory depression within a 6-hour period following anesthesia, were carefully recorded and observed.

**Results:** There were no differences between the two groups in terms of separation anxiety (p>0.05) and post-surgery pain scores (p=0.12). Regarding postoperative agitation, there were significantly more patients in an awake but calm state in the CM group than in the MK (44% vs. 17.64%, p=0.01). The incidence of nausea and vomiting was lower in the CM than in the MK group (47% vs. 76.5%, p=0.02).

**Conclusion:** This study shows that an oral mixture of CM is more suitable as pre-anesthetic medication in pediatric patients undergoing tonsillectomy than a MK.

**Keywords:** Tonsillectomy, pediatric, anesthesia, premedication, midazolam, ketamine, chloral hydrate, meperidine

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***Cite this article as:*** *Naderi N, Emami S, Banifatemi M, Ghadimi M, Shahriari E, Sahmeddini MA. Comparative Analysis of Preoperative Sedation Modalities: Oral Midazolam and Ketamine Versus Chloral Hydrate and Meperidine in Pediatric Tonsillectomy - A Randomized Clinical Trial. Turk Arch Otorhinolaryngol. 2024; 62(3): 113-119*

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**Received Date:** 16-01-2024
**Accepted Date:** 24-07-2024

DOI: 10.4274/tao.2024.2023-12-14

## Introduction

Preanesthetic medication in children should aim to alleviate anxiety and promote a smooth and peaceful separation from their parents (1,2). In addition to its primary objectives, another crucial aim of pre-anesthetic medication before tonsillectomy is to provide effective analgesia post-surgery. Insufficient analgesia following

tonsillectomy can lead to behavioral alterations, restlessness, and vomiting, and may impede the resumption of oral intake (3). A wide range of drugs, administered through various routes such as oral, intramuscular, and intravenous, are presently approved and employed for pre-anesthetic medication in children (4). In context of ambulatory surgeries like tonsillectomy, the optimal choice for premedication in pediatric patients would be a drug that offers prompt and consistent efficacy, minimal adverse effects, and rapid elimination from the body (5, 6). Nevertheless, there is no single drug available that satisfies all of these criteria completely. Furthermore, oral administration is preferred over other routes of administration in pediatric patients as it is non-traumatic and generally more well-received by children (7).

An assortment of drugs, including barbiturates, opioids, benzodiazepines, and ketamine, have been employed as premedication options in pediatric tonsillectomies (8). Certain studies have indicated that a combination of ketamine and midazolam might meet the aforementioned criteria. However, other studies have noted that ketamine could induce prolonged sedation despite its effectiveness in providing satisfactory postoperative analgesia (9-12). In a separate study conducted in pediatric dentistry, a combination of midazolam and meperidine produced favorable outcomes (13). Chloral hydrate is another sedative drug commonly utilized. It is considered safe and exhibits rapid efficacy in alleviating anxiety. However, it lacks analgesic properties, making it less suitable as an ideal premedication option for pediatric tonsillectomy (14, 15). While opioids offer a satisfactory analgesic effect, they pose significant risks, including respiratory depression. Moreover, opioids contribute to an increased occurrence of postoperative nausea and vomiting (PONV), which can be detrimental to pediatric patients undergoing tonsillectomy (16).

The objective of this study was to assess and compare the effectiveness of an oral combination of midazolam and ketamine (MK) versus an oral combination of chloral hydrate and meperidine (CM) as premedication in pediatric patients undergoing tonsillectomy. The primary goals included evaluating the level of sedation before anesthesia and examining postoperative agitation and analgesia. Additionally, the secondary objectives encompassed investigating the potential side effects of the drugs, such as PONV, respiratory depression, and prolonged sedation in the recovery room.

## Methods

This randomized clinical trial was designed as a single-center, double-blind, and parallel-group study, utilizing block randomization. The study was duly registered in the Iranian Registry of Clinical Trials (IRCT2015111611662N8) (https://www.irct.ir/trial/11836 ) and received approval from the Shiraz University of Medical Sciences Ethics Committee (IR.sums.med.rec.1394.351). The research was conducted at Khalili Hospital's operating theater in Shiraz, Iran, from January 2016 to February 2017. The purpose and objectives of the study were thoroughly explained to the parents of the participating children, and written informed consent was obtained from the parents before their inclusion in the trial.

The participants in this study comprised pediatric patients aged 3-7 years, classified as American Society of Anesthesiologists were scheduled for elective tonsillectomy surgery under general anesthesia. Exclusion criteria were applied, and patients were ineligible if they had a history of congenital cardiopulmonary disorders, known allergic reactions to the study drugs, a history of convulsions, brain tumors, high intracranial pressure, hepatic or renal disorders, gastritis, recent use of anxiolytic medications within the past 48 hours, acute upper respiratory tract infection, or if they were undergoing adenotonsillectomy.

In a preoperative holding area, patients received preoperative anesthesia 30 minutes before going into the operating theater. The CM group received chloral hydrate (100 mg/mL) 50 mg/kg and meperidine1.5 mg/kg (10 mg/mL) diluted in cherry juice to a total volume of 5 mL, and the MK mixture group received midazolam (5mg/mL) 0.5 mg/kg and ketamine (50mg/mL) 5 mg/kg diluted in cherry juice to a total volume of 5 ml. These mixtures were administered in syringes identical in appearance that had been labeled either A or B and were prepared by a nurse anesthetist not participating in the study. The patients and the research assessor were not aware of the contents of either syringe.

When the children were separated from their parents to prepare for entering the operating theater, separation anxiety of the children was assessed by a resident of anesthesia who was blinded to study groups, according to a scale of 1=Violent movement, 2= crying, 3= full awake-calm, 4= asleep (17). Separation anxiety was the primary outcome of this study.

When the child was laid down in the operating room, and after the attachment of standard monitors (EKG, noninvasive blood pressure monitor, and pulse oximetry), an angiocatheter No. 22 was inserted. Anesthesia of midazolam 0.03 mg/kg, fentanyl (10mcg/mL) 2 mcg/kg, propofol (10mg/mL) 2 mg/kg, and atracurium (10mg/mL) 0.6 mg/kg was administered through the angiocatheter, then tracheal intubation was performed with a suitable size tracheal tube. Anesthesia was maintained with $O_2$/$N_2O$ (50%/50%) and isoflurane with controlled ventilation. At the end of the operation, the muscle relaxant was reversed with an appropriate dose of neostigmine 0.15mg/kg with atropine 20 mic/Kg, when the patient had spontaneous eye-opening and good muscle strength, tracheal extubation was performed. Then the child was transported to the post anesthesia care unit (PACU).

Five minutes after arriving in the PACU, the emergence of agitation was evaluated by a blinded examiner to the study groups with this scale: 1= severely agitated and difficult to comfort, 2= agitated, 3= asleep, 4= awake but calm (17). Emergence agitation was a secondary outcome of the study.

Other secondary outcomes included: postoperative pain assessed with the Baker-FACES pain scale (18) (Figure 1); PONV recorded according to a scale of 0=no nausea or vomiting, 1=nausea only, and 2=retching and vomiting (19). Also, respiratory rate was recorded, and respiratory depression was defined as a respiratory rate of less than eight breaths per minute. These second outcomes were recorded up to six hours after surgery. Also, if a VAS score higher than 4 was observed, 0.1 mg/kg of morphine was injected.

### Sample Size

The sample size was estimated by setting postoperative agitation as the primary outcome. Assuming the routine premedication (midazolam) success rate was 50%, we calculated that 34 patients in each group would be sufficient to detect an achieved 90% success rate on the postoperative agitation at an alpha threshold of 0.05 with 90% power and 30% dropouts. Eligible patients using the block randomization method (www.sealedenvelope.com) were allocated to the groups in 11 blocks of size 4 and 8. The name of each patient's group was written and prepared in sealed envelopes by a single staff member who had access to the randomization list.

### Statistical Analysis

Data were analyzed using SPSS 21 (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and GraphPad Prism version 9.00 for Windows, (GraphPad Software, Boston, Massachusetts USA), Continuous variables were reported as mean±SD, and independent sample t-test and Mann-Whitney U test were used for analyzing continuous variables. Categorical variables were reported as numbers and percentages, and the chi-square test and Fisher's exact test were used to test the difference in categorical outcome variables. A repeated measure ANOVA test was used for the data obtained over time. P-values less than 0.05 were considered statistically significant and the Bonferroni correction was used for p-values if needed.

## Results

Of the 90 pediatric patients aged 3 to 7 years old scheduled for just tonsillectomy surgery from January 2016 to February 2017, a total of 22 patients were excluded from the study due to pulmonary disorders (n=2), a definite diagnosis of convulsion disorder (n=5), presence of congenital heart disease (n=3) and acute upper respiratory tract infection (n=9), or declined to participate (n=3). Thus, a total of 68 patients were enrolled in the study and were randomly allocated into two intervention groups (Figure 2).

Table 1 shows the demographic characteristics data of patients. There were no significant differences in age (p=0.18), weight (p=0.34), sex (p=0.55), duration of anesthesia (p=0.21), and surgery duration (p=0.32) between the two groups (p>0.05).

The comparison of separation anxiety scores in Table 2 shows that there was no significant difference in separation anxiety scores between the groups (p>0.05). For clarity, each condition is accompanied by its corresponding p-value: sleep (p=0.42), fully awake and calm (p=0.80), crying (p=0.49), and violent movement (p>0.99).

Furthermore, there were no significant differences in the postoperative agitation scores for asleep (p=0.80), agitated (p=0.33), and severely agitated difficult-to-comfort (p>0.99) statuses between the two groups (p>0.05). Only the number of patients who were awake but in a calm state was higher in the CM group than the MK group (44% vs. 17.64%, p=0.01) (Table 3).

Comparison of the incidences of nausea and vomiting between the groups over time after the operation showed that the time effect (p=0.21) and interaction between time and groups (p=0.84) were not significant (p>0.05). Only the group effect was significant (p=0.02) (Figure 3).

In the cumulative analysis of PONV between the groups, it was found that the CM group had a lower PONV with an incidence of 47% compared to the MK group, 76.47% (p=0.02).


**Figure 1.** The Baker-FACES pain scale

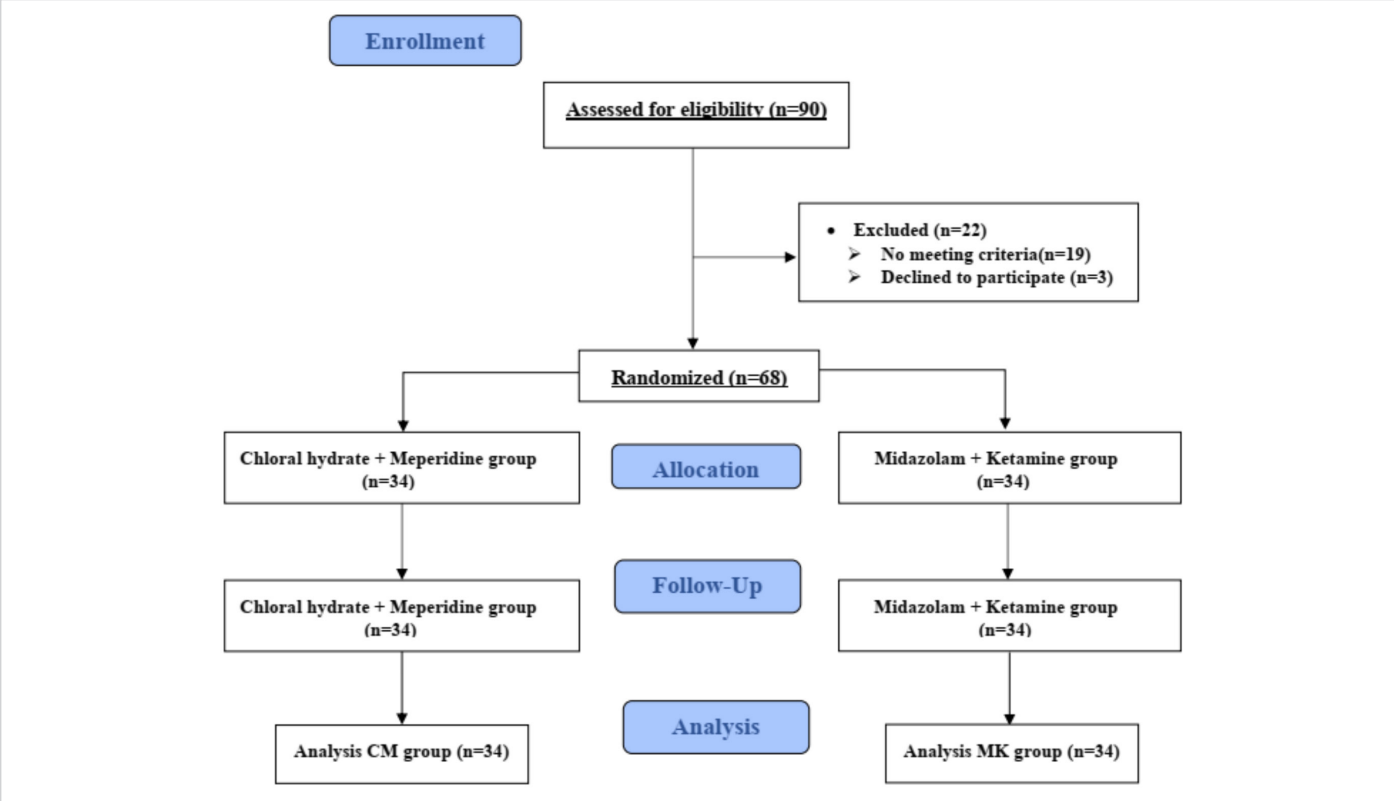



**Figure 2.** Flowchart and consort diagram of patients

**Table 1.** Demographic characteristics of pediatric patients in the studied groups

| | CM group (n=34) | MK group (n=34) | p-value |
|---|---|---|---|
| Age (year) | 5.21±1.23 | 4.82±1.14 | 0.18 |
| Weight (Kg) | 17.68±3.44 | 16.85±3.64 | 0.34 |
| Sex; male | 22 (65) | 21 (62) | 0.55 |
| Surgery duration (min) | 35.89±10.2 | 38.19±8.9 | 0.32 |
| Anesthesia duration (min) | 45.73±13.25 | 49.55±12.11 | 0.21 |

Values are presented as mean ± standard deviation or numbers (percentages)

CM: Chloral hydrate and meperidine, MK: Midazolam and ketamine,

**Table 2.** Separation anxiety scores in the studied groups

| | CM group (n=34) | MK group (n=34) | p-value |
|---|---|---|---|
| Sleep | 11 (32.35) | 8 (23.52) | 0.42 |
| Full awake-calm | 19 (55.88) | 20 (58.82) | 0.80 |
| Crying | 4 (11.76) | 6 (17.64) | 0.49 |
| Violent movement | 0 (0.00) | 0 (0.00) | > 0.99 |

The values are presented as numbers (percentages)

CM: Chloral hydrate and meperidine, MK: Midazolam and ketamine

**Table 3.** Postoperative agitation score of the children in both groups

| | CM group (n=34) | MK group (n=34) | p-value |
|---|---|---|---|
| Asleep | 16 (47) | 24 (70.5) | 0.08 |
| Awake but calm | 15 (44) | 6 (17.64) | 0.01* |
| Agitated | 1 (2.94) | 3 (8.82) | 0.33 |
| Severely agitated and difficult to comfort | 0 (0%) | 0 (0%) | >0.99 |

Values are presented as numbers (percentages)

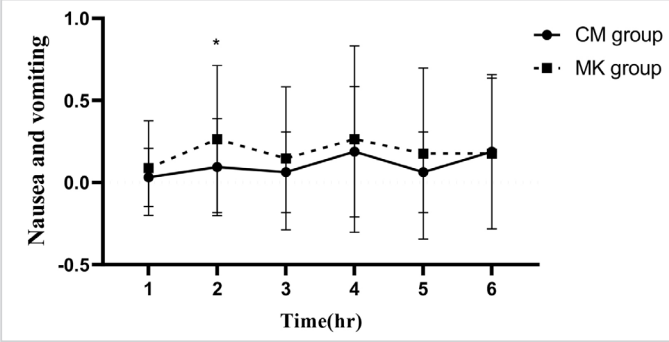
*Indicates significant p-value

CM: Chloral hydrate and meperidine, MK: Midazolam and ketamine

Figure 4 shows postoperative pain intensity in the studied group over time.

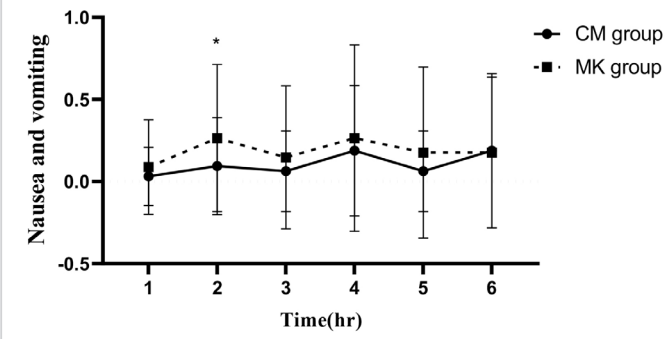
The repeated measurement analysis results for postoperative pain intensity indicate that the pain had decreased after the surgery over time in both groups ($p<0.001$), and the premedication did not affect the pain intensity of patients ($p=0.12$). Therefore, patients in both groups had the same pain intensity experience after the surgery.

It should be noted that during the study, no respiratory depression was observed in any of the patients. Also, the two groups were not different in taking morphine (4±2 vs. 3.88±2, $p=0.79$).




Time effect =0.21, interaction (time* group) =0.84, group effect =0.02
Bonferroni correction p-value =0.008
$p_{t=2}$ <0.001
*Indicates significant p-value
CM: Chloral hydrate and meperidine, MK: Midazolam and ketamine

**Figure 3.** Postoperative nausea and vomiting in the studied groups over time




Time effect<0.001, interaction (time* group)= 0.046, group effect=0.129
CM: Chloral hydrate and meperidine, MK: Midazolam and ketam

**Figure 4.** Postoperative pain intensity in the studied groups over time

## Discussion

This randomized clinical trial furnishes substantiation indicating that an oral combination of CM elicited a greater sense of comfort and alertness in children upon emergence from anesthesia when compared to an oral combination of MK. Moreover, the CM combination demonstrated superior efficacy as a premedication.

Historically employed as a premedication in pediatric contexts, oral midazolam lacks the requisite analgesic efficacy crucial in the aftermath of a painful procedure. Numerous investigations have explored the impact of a combination of MK. Banerjee et al. (20) demonstrated that such a composite formulation proved more efficacious than either constituent administered in isolation. Funk et al. (21) observed analogous findings. Due to the inherent absence of analgesic properties in midazolam alone, these investigations incorporated ketamine alongside midazolam to induce analgesia. Furthermore, the concurrent administration of midazolam served to diminish the emergence phenomena associated with oral ketamine (21). Nevertheless, oral premedication necessitates a longer duration to induce sedation. Consequently, to expedite the onset, a higher dose of the drug is required. However, this escalated dosage results in prolonged postoperative sedation and hinders timely discharge from the recovery room (21). Oral ketamine undergoes a pronounced first-pass effect in the liver, leading to the formation of nor-ketamine. This metabolite of ketamine plays a role in the analgesic effects observed after the administration of oral ketamine (22, 23).

In our investigation, we observed concordant findings with Funk et al. (21) study, notwithstanding the analgesic impact of ketamine in conjunction with midazolam. This combination induced increased drowsiness among patients in the recovery room, resulting in a delay in discharge-a phenomenon not observed with the CM mixture.

While oral chloral hydrate has been employed for sedation in pediatric patients, akin to midazolam, it lacks analgesic properties (24,25). As a consequence, chloral hydrate emerges as the preferred sedative for pediatric patients undergoing diagnostic procedures that do not necessitate analgesic intervention (24).

Nathan and Vargas (13) ascertained that augmenting midazolam with meperidine enhanced both the effectiveness and the duration of midazolam in pediatric patients. Furthermore, their investigation revealed that premedicated patients exhibited diminished postoperative pain and displayed reduced distress upon separation from their parents. In our investigation, we supplemented chloral hydrate with meperidine to elicit a combined analgesic and sedative effect. Our findings indicate that the amalgamation of meperidine and chloral hydrate induced drowsiness in children upon separation from their parents, facilitating a smooth induction of anesthesia. After the surgical procedure, the patients exhibited prompt wakefulness and comfort, enabling expedited discharge from the recovery room.

PONV following tonsillectomy represent a significant concern due to its potential to elevate the risk of postoperative bleeding, pulmonary aspiration, and the necessity for hospitalization (26). Nonetheless, in our investigation, the incidence of PONV was lower with the combination of CM when compared to the combination of MK. Although the statistical analysis did not show a significant difference in pain intensity between the groups, the results reveal that children in the MK group experienced more pain from two hours post-surgery until the end of the study (six hours after surgery) compared to the CM group. We believe that even though the difference between the pain levels is small and not statistically significant, it could be clinically important and might lead to a higher incidence of PONV in the CM group, given the high sensitivity of children. This observation

highlights an additional advantage of the CM combination over the midazolam-ketamine combination.

### Study Limitations

This study possesses certain limitations. Firstly, a more extended observation period, ideally encompassing at least 24 hours, is warranted to thoroughly assess the sustained analgesic efficacy of these mixtures. Secondly, future investigations would benefit from an augmented sample size to discern potential further distinctions between the two mixtures. Thirdly, the examination of drug-related side effects, such as an elevation in muscle tone and salivation in the ketamine-midazolam group, and potential interference with surgical techniques should be taken into consideration.

## Conclusion

In summary, this investigation demonstrated comparable effects between an oral mixture of MK and a mixture of CM concerning anxiety levels upon separation from parents and anesthesia induction. Each group was administered a combination of sedative drugs for pre-operative sedation and analgesic drugs for postoperative pain. This was done to assess the level of sedation before anesthesia and to observe any postoperative restlessness and pain relief.

Nevertheless, following the emergence from anesthesia, the oral combination of CM could exhibit a superior outcome by promoting wakefulness and greater comfort in patients, in contrast to the oral mixture of MK, which induced increased drowsiness during the emergence phase, consequently leading to delayed discharge from the recovery room. Moreover, the oral combination of CM could have better efficacy in managing agitation in the early postoperative period compared to the combination of MK.

### Ethics

**Ethics Committee Approval:** The study was duly registered in the Iranian Registry of Clinical Trials (IRCT2015111611662N8) (https://www.irct.ir/trial/11836 ) and received approval from the Shiraz University of Medical Sciences Ethics Committee (IR.sums.med.rec.1394.351).

**Informed Consent:** The study did not require patient consent as it was based entirely on the university clinic's database of questions obtained from publicly available online medical textbooks.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: N.N., S.E., E.S., M.A.S Concept: N.N., S.E., M.B., M.G., E.S., Design: N.N., S.E., M.B., M.G., E.S., Data Collection and/or Processing: N.N., M.B., M.G., Analysis and/or Interpretation: M.B., E.S., Literature Search: S.E., Writing: N.N., E.S.

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

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

### Main Points

- There was no significant difference in separation anxiety scores between the chloral hydrate and meperidine (CM) or midazolam and ketamine (MK) groups.
- An oral mixture of CM was found better than a MK in postoperative agitation in pediatric patients undergoing tonsillectomy.
- The CM group had less postoperative nausea and vomiting than the MK group.
- The patients in both groups experienced the same levels of pain intensity after the surgery.

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# An Unusual Acute Otitis Media Complication: Luc's Abscess

Case Report

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**Abstract**

Otitis media, a common childhood disease, can lead to serious complications such as acute mastoiditis and, rarely, Luc's abscess, with life-threatening consequences. Luc's abscess, a rare but severe complication, can occur without acute mastoiditis. This case report details a case of Luc's abscess in a 14-year-old girl with acute otitis media, presenting with ear pain, facial swelling, and hearing loss. Treatment involves a multidisciplinary approach, considering factors like age and abscess extent. Though there is no established standard treatment, this case emphasizes the need for prompt recognition and appropriate intervention to prevent severe complications. This case report emphasizes the importance of tailored, timely interventions for optimal outcomes in affected children.

**Keywords:** Otitis media, complication, mastoiditis, pediatric otorhinolaryngology, case report

## Introduction

Otitis media is a prevalent pediatric condition, frequently diagnosed and treated in clinical practice. While often self-limiting, it can lead to severe complications such as acute mastoiditis, subperiosteal abscess, facial nerve paralysis, and meningitis, given its anatomical proximity to critical structures (1,2).

Acute mastoiditis was a common complication of acute otitis media before the advent of antibiotics, which significantly reduced its incidence. Despite this, acute mastoiditis can still progress to life-threatening situations if the infection is not controlled by antibiotics (3,4). Subperiosteal abscesses of otogenic origin typically result from the spread of infection into the subperiosteal space, often due to cortical bone erosion secondary to acute mastoiditis. Bezold's abscess involves the sternocleidomastoid muscle, Citelli's abscess is in the digastric triangle, and Luc's abscess, beneath the temporalis muscle, is particularly rare and due to its rarity, diagnosing and treating this condition may be complicated (2). Luc's abscess is distinct in that it usually arises not from the mastoid bone but from a middle ear infection spreading through the pre-existing notch of Rivinus in the external auditory canal, often without concurrent acute mastoiditis (1). A rare route to the temporal fossa is via the pneumatized zygomatic arch, leading to subperiosteal abscesses associated with acute mastoiditis. In these cases, temporal bone computed tomography (CT) is invaluable for diagnosis.

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***Cite this article as:*** *Akpınar M, Demirci B. An Unusual Acute Otitis Media Complication: Luc's Abscess. Turk Arch Otorhinolaryngol. 2024; 62(3): 120-123*

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**Received Date:** 17-02-2024
**Accepted Date:** 24-09-2024

DOI: 10.4274/tao.2024.2024-2-4

We present a case of Luc's abscess with mastoid bone involvement as a complication of acute otitis media. Informed consent and ethics committee approval were obtained for presentation of this case.

## Case Presentation

A 14-year-old girl presented to the emergency department with a seven-day history of left ear pain and hearing loss, accompanied by swelling on the left side of her face for the past three days. She also experienced high fever, fatigue, and reduced oral intake. Despite five days of antibiotic treatment (amoxicillin-clavunate 1000 mg, 2x1), there was no improvement. The patient had no previous medical history related to ear issues or trauma.

Upon examination, trismus and swelling from the left temporal region extending towards the cheek and lower eyelid were observed (Figure 1A). Severe edema in the left external ear canal hindered the evaluation of the tympanic membrane. Laboratory analysis indicated leukocytosis, neutrophilia, and elevated C-reactive protein. A pure tone audiogram revealed moderate conductive-type hearing loss in the left ear. CT scans showed opacification of the left middle ear cavity consistent with acute otitis media, along with mucosal thickening and fluid-filled mastoid air cells indicating mastoiditis. A focal defect in the left temporal bone's mastoid cells was observed, leading to widespread edema and inflammation spreading to the left face (Figures 2A and 2B). No other significant feature was found in the evaluation of the same patient by ophthalmology consultation.

The patient was diagnosed with otitis media complicated by Luc's abscess and was hospitalized in our clinic. All written consent was taken from the patient's parents as she was aged under 18. She was given a start of intravenous (IV) antibiotic (ceftriaxone 1 gr, 3x1) treatment by the recommendation of the infectious disease clinic, moxifloxacin ear drop, and Burow's solution (aluminum subacetate) which was applied to an ear-wick for a day as well as with analgesic and IV fluid replacement therapy. Emergency surgery involved myringotomy, Shepard grommet insertion, and abscess drainage. Approximately 50-100 cc of pus was drained. The surgical area was washed with RIF® (rifampicin 250mg, Koçak, Türkiye) and sodium chloride 0.9% solution. Penrose drain was embedded in the bottom of the temporalis muscle to allow further pus to drain. The patient quickly recovered post-surgery, with a resolution of symptoms and swelling within 48 hours (Figure 1B). Cultures of purulent material showed no growth due to prior antibiotic treatment.

Different surgical approaches exist for acute mastoiditis complications, with some departments performing mastoidectomy concurrently with ventilation tube insertion and abscess drainage. In this case, IV antibiotic treatment continued for 14 days after surgical drainage. The patient was discharged and scheduled for a second-stage mastoidectomy, which was later canceled due to parental refusal. A postoperative one-month follow-up revealed that the ventilation tube was in place, and the patient's hearing had fully recovered.

## Discussion

Luc's abscess is a rare but serious complication of otitis media primarily observed in children. Its rarity can be attributed to the effectiveness of antibiotic therapy in


**Figure 1.** Preoperative (1A) and postoperative 2nd week (1B) images of the patient

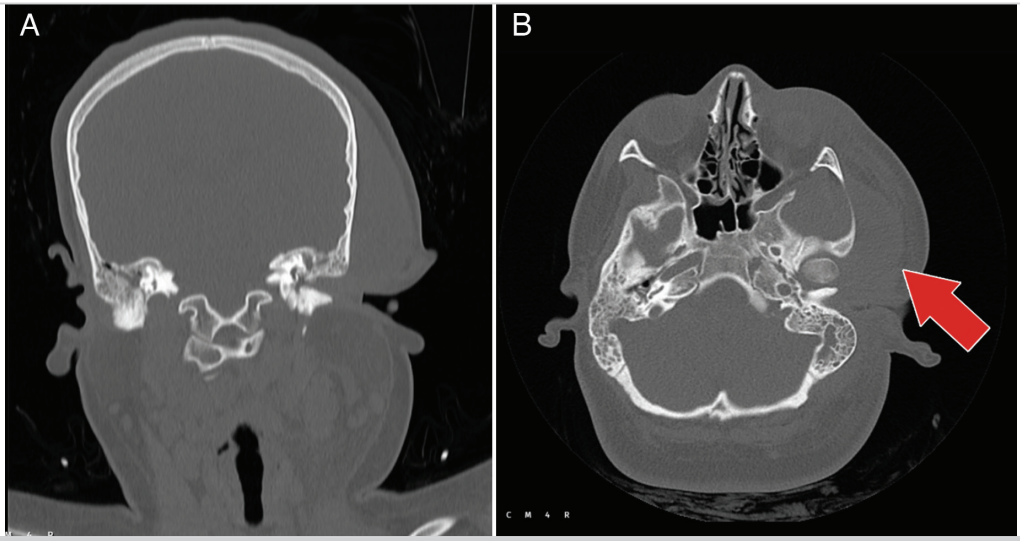


**Figure 2.** In the patient's preoperative CT scan, the left middle ear cavity was observed to be opaque with soft tissue density material (2A) compatible with acute otitis media, and further widespread edema and inflammation symptoms spreading to the left half of the face (2B)
CT: Computed tomography

treating most cases of otitis media before complications arise. However, despite its rarity, healthcare professionals must remain vigilant in recognizing this condition due to its potentially life-threatening consequences such as acute mastoiditis, subperiosteal abscess, facial paralysis, and meningitis (4,5).

Early diagnosis and prompt treatment are essential to prevent serious complications. Symptoms typically include persistent ear pain, fever, tenderness, and ear discharge. Diagnosis is based on clinical evaluation, imaging studies, and microbiological tests. Managing Luc's abscess is complex due to the lack of a standard treatment method. The best approach depends on factors such as age, abscess size, complications, and individual patient characteristics, requiring a personalized treatment plan that could include medication, surgery, or supportive care (6,7).

## Conclusion

Luc's abscess is a rare complication of otitis media in children, necessitating early recognition and appropriate treatment due to its potentially life-threatening complications. The most accurate treatment method for Luc's abscess has yet to be defined due to the low incidence of the case. Despite the absence of a definitive treatment approach, combined medical and surgical management is typically employed. Prompt diagnosis, proper management, and close monitoring are essential to ensure the best possible outcomes for affected children.

### Ethics

**Informed Consent:** Informed consent and ethics committee approval were obtained for presentation of this case.

### Footnotes

### Authorship Contributions

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

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

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

### Main Points

- **Rare Complication of Otitis Media:** Luc's abscess is highlighted as a rare but serious complication of otitis media, particularly in children. This emphasizes the importance of recognizing the condition early to prevent potentially life-threatening consequences.
- **Lack of Defined Treatment Protocol:** Defining a standardized treatment approach for Luc's abscess is challenging due to its low incidence. This suggests a need for further research and clinical guidelines to optimize patient outcomes.
- **Multidisciplinary Approach:** Despite the absence of a definitive treatment protocol, it is important to have a multidisciplinary approach involving both medical management and surgical intervention. This approach aims to address the complex nature of Luc's abscess and mitigate its complications effectively.
- **Importance of Prompt Diagnosis and Management:** This case report stresses the critical role of prompt diagnosis, proper management, and close monitoring to ensure the best possible outcomes for children affected by Luc's abscess. This highlights the significance of early intervention and vigilant care in addressing this condition.

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