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IL-8 and IFN-γ as Preoperative Predictors of the Outcome of Tonsillectomy

Alicia Seethaler[1], Markus Stenner, MD[1], Annika McNally, MSc[2], Claudia Rudack, MD[1], Johannes Roth, MD[2], Thomas Vogl, PhD[2], and Christoph Spiekermann, MD[1,2]

Abstract

Objectives: Tonsillectomy (TE) and tonsillotomy (TO) due to recurrent episodes of acute tonsillitis (RAT) belong to the most frequent surgical procedures. However, an adequate objective marker predicting the outcome of TE/TO preoperatively is missing. **Methods:** Patients with RAT who underwent TE/TO (n = 31) were included in this pilot study. A panel of cytokines and chemokines in serum and saliva were determined preoperatively. Health-related quality of life was assessed pre- and postoperatively by the Tonsillectomy Outcome Inventory-14. **Results:** Health-related quality of life improved significantly after surgery. Increased serum levels of interleukin-8 (IL-8) and interferon gamma (IFN-γ) are associated with a less successful outcome. No correlation between the number of acute tonsillitis episodes and the health-related quality of life after TE or TO could be observed. **Conclusions:** Tonsillectomy and TO improve health-related quality of life independently from the number of past acute tonsillitis episodes. Interleukin-8 and IFN-γ in serum may serve as promising markers, predicting the benefit of TE or TO for patients preoperatively.

Keywords

tonsillectomy, tonsillotomy, cytokines, alarmins, outcome, biomarker

Introduction

Acute tonsillitis is one of the most frequent reasons patients seek otolaryngology or primary medical care consultation.[1] In some cases, patients have recurrent episodes of acute tonsillitis (RAT), also known as chronic tonsillitis, which is associated with a high frequency of missed work or school days. Hence, RAT has an important influence on quality of life (QoL) and requires a substantial utilization of medical and socioeconomic resources.[1,2]

Tonsillectomy (TE) and tonsillotomy (TO) are proven therapy approaches for RAT. Currently, a decision in favor of surgery is made based on the number of acute tonsillitis episodes that were treated with antibiotics within the previous 3 years.[3,4] In clinical practice, the identification and differentiation between viral and bacterial tonsillitis is not reliable. Therefore, the current criteria are not appropriate in identifying patients who could benefit from TE/TO and objective preoperative markers to enable this are still missing.[1,5]

The outcome of TE mainly depends on the patient's subjective perception of symptom reduction and the perceived improvement of QoL. Questionnaires have proven valuable as patient-reported outcome assessment instruments in various diseases and procedures. In cases of TE/TO, the Tonsillectomy Outcome Inventory 14 (TOI-14) represents an established outcome assessment instrument. The TOI-14 is a valid and reliable disease-specific questionnaire for patients with RAT that measures various dimensions of QoL and postoperative outcome. It explicitly integrates socioeconomic issues, such as throat discomfort, general health, use of recourses, and sociopsychological restrictions.[6]

As a part of the mucosa-associated lymphoid tissue and the Waldeyer ring, the palatine tonsils are considered important

[1] Department of Otorhinolaryngology—Head and Neck Surgery, University Hospital Münster, Germany
[2] Institute of Immunology, University Hospital Münster, Germany

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Corresponding Author:
Christoph Spiekermann, MD, Department of Otorhinolaryngology, University Hospital Münster, Kardinal-von-Galen-Ring 10, 48149 Münster, Germany.
Email: christophotto.spiekermann@ukmuenster.de

components of the immune defense against oropharyngeal pathogens.[7] Polymicrobial infection with an insufficient host defense is the most frequent reason for tonsillar inflammation.[8] Hence, inflammatory reactions are induced by a release of various cytokines and chemokines, such as tumor necrosis factor-alpha (TNF-α), interferon (IFN)-γ, interleukin (IL)-1β, IL-6, IL-8, IL-10, IL-12, and so on.[1,9-11]

The heterodimeric calcium-binding complex S100A8/A9, expressed by neutrophil granulocytes, monocytes, and different keratinocytes, belongs to a group of damage-associated molecular patterns.[12] Increased levels of S100A8/A9 have been observed in various acute and chronic diseases.[13,14] Recently, increased levels of S100A8/A9 were observed in serum and saliva of patients having a peritonsillar abscess.[15,16] The aim of the present study was to identify preoperative objective markers that could aid in predicting the outcome and success of TE/TO in patients with recurrent acute tonsillitis.

Materials and Methods

Study Population

Patients who underwent TE or TO due to recurrent tonsillitis (n = 31) were enrolled in this pilot study. As according to the national guidelines, TO was performed in patients with tonsil hyperplasia. The study population had a median age of 26 years (range: 13-59 years) and consisted of 15 male and 16 female patients (male to female ratio, 0.94:1). The median follow-up was at 23 months (range: 16-28 months). Preoperative study enrollment and surgery were conducted during an asymptomatic interval without acute inflammation.

Ethical Approval

The present study was performed according to ethical principles, including the World Medical Association Declaration of Helsinki (version 2002) and supplemented by requirements constituted by the Department of Otorhinolaryngology, Head and Neck Surgery, of Muenster University Hospital. The study has been approved by the institutional review board [2015-217-f-S]. Written informed consent was obtained from all patients.

Acquisition of Sera and Saliva Samples

In order to isolate the serum fraction, blood was allowed to clot and centrifuged at 2000*g* for 10 minutes within 2 hours after acquisition. The required saliva was acquired either by the use of Untreated Salivette (Sarstedt, Nümbrecht, Germany, 51.1534) according to manufacturer's manual or by collecting it in 50 mL Falcon tubes. The saliva was than centrifuged at 1000*g* for 15 minutes. The saliva and sera samples were both aliquoted and stored at −20°C until analysis.

Analysis of Chemokines, Cytokines, and Soluble Proteins

Cytokines and chemokines in serum and saliva were quantified by LEGENDplex assay ''Human Inflammation Panel'' (BioLegend, California, USA) in accordance with the manufacturer's datasheet. The ''Human Inflammation Panel'' allows for a simultaneous quantification of IL-1β, IL-6, IL-8, IL-10, IL-12p70, IL-17A, IL-18, IL-33, IFN-α, IFN-γ, monocyte chemoattractant protein-1 (MCP-1), and TNF-α in fluids. The NAVIOS Flow Cytometer (Beckmann Coulter, Brea, California) was utilized to measure fluorescent signal intensities. A sandwich enzyme-linked immunosorbent assay for human S100A8/A9 was used to detect S100A8/A9 concentrations as described previously.[17]

Outcome of Patients With Recurrent Tonsillitis

The QoL and outcome of the patients were measured pre- and postoperatively using the TOI-14, a disease-specific questionnaire for patients with RAT. The TOI-14 represents a valid and reliable questionnaire with a high sensitivity to detect clinical improvement after surgery. It consists of 14 questions dealing with throat discomfort, general health, use of resources, and sociopsychological restrictions. Answers were given on a 6-point Likert scale with higher scores indicating a higher burden of disease.[6] Additionally, the patients were asked postoperatively whether they would recommend the same surgery to patients/friends/family members with the same symptoms. These answers were given using the same 6-point Likert scale as mentioned above. A more or equal than 50% decrease in the TOI-14 score was considered a successful outcome. These patients with major benefits of surgery were grouped to the major cohort whereas patients with a decrease less than 50% in the TOI-14 score and thus minor benefits of surgery were grouped to the minor cohort.

Statistical Analysis

The results are described as mean values ± standard error of the mean or mean value ± standard deviation (mean ± SD) as indicated in the figures and text. Spearman correlation coefficients (r_{sp}) were determined in order to describe the correlations between variables and were considered to be either low ($0.2 < r_{sp} \leq 0.5$), good ($0.5 < r_{sp} \leq 0.8$), or excellent ($0.8 < r_{sp} \leq 1.0$). The Student *t* test was used to detect significant differences in parametric results and the Mann-Whitney *U* test was performed to analyze differences between nonparametric groups. Values of $P < .05$ are considered to be significant. Statistical advice was given by the Institute of Biometrics and Clinical Research at the University of Münster. Statistical analyses were performed with IBM SPSS Statistics version 25 and SigmaPlot version 12.

Results

Quality of Life

The outcome and QoL were assessed pre- and postoperatively. The median follow-up was 23 months with a range from 18 to 28 months. Preoperatively, the patients had RAT associated with restrictions to QoL represented by a TOI-14 score of 35.8 ± 12.2 (mean ± SD). Postoperatively, a significant

decrease in the TOI-14 score could be observed in comparison to the preoperative assessment (8.4 ± 9.0, mean ± SD, $P < .001$; Figure 1). This indicates a lower burden of disease and an improvement of the patients' QoL after surgery.

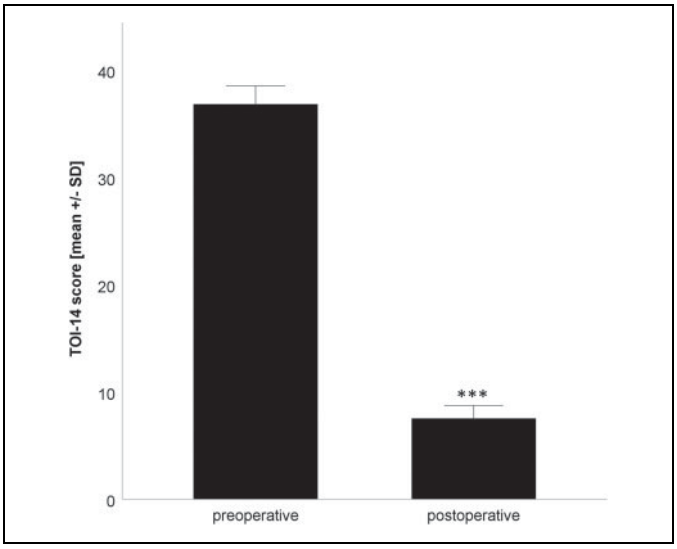

Figure 1. Tonsillectomy Outcome Inventory-14 (TOI-14) scores. Compared to postoperative scores, patients undergoing tonsillectomy or tonsillotomy show significantly increased TOI-14 score values preoperatively. Tonsillectomy or tonsillotomy cause an improvement of health-related quality of life (***$P < .001$).

Cytokines and Chemokines

The salivary and serum baseline levels of IL-1β, IFN-α, IFN-γ, TNF-α, MCP-1, IL-6, IL-8, IL-10, IL-12p70, IL17A, IL-18, IL-23, IL-33, and S100A8/9 were quantified and the baseline levels were compared dependent on the change in the TOI-14 scores. Therefore, patients were assigned to 2 groups according to the gauged surgical success based upon their change in TOI-14 score. A TOI-14 score difference above or equal to 50% was considered to indicate a more successful surgery (major), whereas a difference lower than 50% indicated a less successful surgery (minor). Comparing these groups, no significant differences could be detected in salivary cytokine, alarmin, and chemokine levels. However, in serum, significantly increased levels of IFN-γ (minor: 10.7 ± 4.8 pg/mL, major: 2.1 ± 0.9 pg/mL, $P = .007$) and IL-8 (minor: 12.5 ± 0.9 pg/mL, major: 6.5 ± 0.6 pg/mL, $P = .005$) could be observed in the group with the less successful outcome (Figure 2A and B).

Recurrent Episodes of Acute Tonsillitis

During the year leading up to surgery, patients had a median of 4 RAT episodes (range: 1-8 episodes). Two years prior to surgery, the frequency of RAT episodes was also around 4 (range: 0-12). However, 3 years prior to surgery, the mean number of RAT episodes was about 2 (range: 0-7). In total, the patients had 9 RAT episodes in median over the last 3 years with a range from 1 to 21 episodes. No correlation was detected

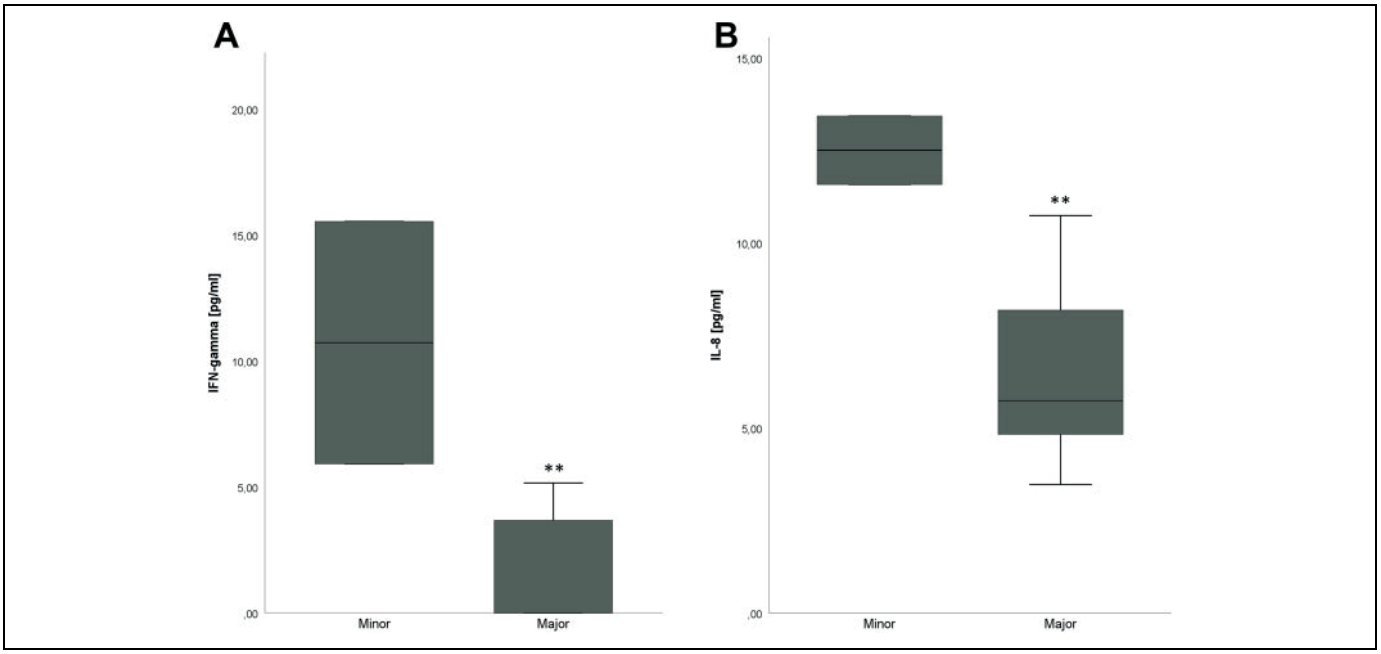

Figure 2. Cytokine levels in serum. Significant higher levels of IFN-γ (A) and IL-8 (B) were observed in serum of patients who had a less than 50% (minor) reduction in their TOI-14 score compared to the patient group who had a higher than/equal to 50% (major) reduction in their TOI-14 score. Lower IL-8 and IFN-γ a levels in serum are associated with a higher improvement of health-related quality of life after tonsillectomy or tonsillotomy in patients with recurrent tonsillitis (**$P < .01$). IFN-γ indicates interferon gamma; IL-8, interleukin-8; TOI-14, Tonsillectomy Outcome Inventory-14.

between the amount of RAT episodes and the change in the TOI-14 score.

Discussion

This is the first report on the use of objective markers to predict the outcome of TE/TO in patients with RAT. Tonsillectomy/TO are both proven therapy approaches for treating patients with RAT. However, the criteria used to decide in favor of or against surgery are still a source of controversy since several biases and disadvantages are associated with them. Currently, a decision is based on the frequency of RAT episodes. Therefore, a preoperative objective marker to aid in this decision is missing. In this study, we addressed this challenge and were able to demonstrate that the number of RAT episodes experienced during the 3 years prior to surgery had no influence on the patient-reported outcome of TE/TO, and that higher levels of IL-8 and IFN-γ in serum are associated with less improvement in QoL after TE/TO.[3,4,18]

As mentioned above, a decision in favor of surgery is made based on the number of acute tonsillitis episodes that were treated with antibiotics within the previous 3 years. In clinical practice, the diagnosis of bacterial tonsillitis is contingent on a physical examination and a medical history taking. Both of these components may be influenced by inaccurate medical documentation and incorrect/incomplete information given by the patient leading to a false estimation of the frequency of bacterial tonsillitis in clinical practice.[19,20] Furthermore, in regard to the medical examination, it can be assumed that many diagnoses of bacterial tonsillitis are incorrect due to the high percentage (50%-80%) of viral pathogens present in acute tonsillitis.[1,21] Although throat swab cultures are highly sensitive, most of the pathogens detected are part of the healthy flora and can also be observed in asymptomatic carriers.[1,22] A rapid antigen test is also an unreliable method to determine the cause of tonsillitis due to its very low sensitivity in diagnosing bacterial tonsillitis.[22] Lastly, using Centor criteria to assess the probability of a Group A streptococcus infection is also not an appropriate tool in distinguishing between a viral and a bacterial infection.[23,24] Therefore, inaccurate assessment of bacterial tonsillitis results in the inappropriate prescribing of antibiotics.[1,22]

Several reports have demonstrated the benefit of TE/TO in patients with recurrent tonsillitis, and even in patients with recurrent sore throat episodes. As the number of these episodes decreased following TE/TO, the use of antibiotics and the number of missed work and school days also declined. Consequently, a significant improvement in QoL, patient satisfaction and outcome, as well as a reduced need for medical resources was observed.[2,25-27] In our study, we could show that patients with RAT benefited from TO/TE regardless of the etiology of tonsillitis. Nevertheless, possible risks of surgery such as postoperative hemorrhage, morbidity, and infections must be weighed against these benefits. Therefore, an objective instrument providing an appropriate patient selection is missing. We show that the frequency of RAT is not the deciding factor for or against surgery in our study, since patients with fewer episodes of recurrent tonsillitis (viral or bacterial etiology) also benefit from this surgery. Therefore, the existing criteria used for TE/TO in patients with RAT are not sufficient to identify patients who could benefit from this surgery.

The outcome of surgery or a medical intervention mainly depends on the patient's subjective satisfaction. Thus, patient-reported outcome measures (PROMs) are important components used to assess the success of therapy approaches, whose outcome cannot be sufficiently represented by clinical parameters.[28,29] In the present study, we used the TOI-14, a disease-specific PROM for RAT, to evaluate the outcome after TE/TO. Prior to this study, a systematic literature review was conducted to identify valid and reliable outcome assessment instruments evaluating the health-related QoL after TE and TO. Based on this systematic review, the disease-specific questionnaire TOI-14 was selected since the TOI-14 is the only reliable and valid questionnaire that measures health-related QoL in patients with recurrent tonsillitis.[30]

Patients were divided into 2 groups based on the results of this evaluation (TOI-14 score difference $<50\%$ or $\geq 50\%$) in order to identify patients who most benefited from surgery. In the evaluation that patients received after surgery, they were asked whether they would recommend the same surgery to other patients/friends/family members with the same symptoms. Most patients in this study stated that they would recommend this surgery to other patients. In addition, patients with a reduction in TOI-14 score $<50\%$ also benefited from surgery and therefore, these patients stated that they would also recommend surgery to others. Some patients, however, would strongly discourage others from receiving this surgery due to their complaints of severe postoperative pain and postoperative hemorrhage. Despite their negative evaluation of recommending surgery to others and their postoperative pain and hemorrhage, these patients still experienced a significant improvement in their QoL after surgery.

In regard to measuring the postoperative outcome, some patient may have negatively rated the outcome since the postoperative period has not been clearly defined in the survey. Therefore, the evaluation may have been influenced by the immediate postoperative period (short-term outcome), associated with postoperative pain, swelling, hemorrhaging, and temporary restrictions, rather than by the long-term outcome. No cutoff value exists for the TOI-14 and no classification exists on which one can speak of a low, moderate, or high restriction of the QoL. Therefore, we had to set a cutoff in advance and then decided on the mean. However, this cutoff might be too strict from a clinical perspective because patients with a TOI-14 score less than 50% also profited from and would further recommend surgery.

In our search to identify preoperative objective markers that could aid in predicting the outcome and success of TE/TO in patients with RAT, we could show that increased levels of IL-8 or IFN-γ in serum of patients with RAT are interestingly associated with less improvement/worse outcome after TE/TO. Generally, IL-8 is produced by endothelial cells, fibroblasts,

macrophages/monocytes, and neutrophils. It is a chemotactic factor for T-lymphocytes and neutrophils which can be observed in inflamed tonsillar tissue.[30] Because of its association with IL-1, TNF-α-, bacterial DNA, and lipopolysaccharide, IL-8 expression in tonsils may depend on the toll-like receptor pathway.[31-33] Interleukin-8 is involved in many inflammatory diseases and it is highly expressed in areas of ulceration and necrosis. Accordingly, high levels of IL-8 were observed in ulcerative tonsillitis, whereas low levels of IL-8 were observed in tonsils with follicular hyperplasia.[31,34] In a peritonsillar abscess, IL-8 is mainly expressed by crypt epithelium and neutrophils during acute inflammation in vivo.[32] Previous studies have shown that infected palatine tonsils primarily produce Th1-type cytokines, including IFN-γ and TNF-α. Later on, they produce Th2-type cytokines (IL-4, IL-6 etc). However, compared to adenoids, the cellular immune response in the palatine tonsils is stronger than the humoral immune response.[35,36]

High levels of IL-8 and IFN-γ in serum may indicate concomitant or other systemic diseases, such as respiratory syncytial virus infection, which continue to have a negative impact on the patient's QoL after TE/TO.[37] Therefore, it may be essential to check for and treat other infections or diseases prior to surgery in patients with high serum levels of IL-8 and IFN-γ, in order to improve the outcome of TE/TO. Another possible approach to ensure a good outcome of surgery would be to only perform surgery on patients with low IL-8 and IFN-γ serum levels. However, this proposition would need further confirmation and will be the subject of further prospective investigation. Furthermore, the causal relation and the influence of IL-8 and IFN-γ on the pathogenesis of recurrent tonsillitis need further investigation.

Additional studies with larger sample sizes are necessary to confirm the data of this study. Larger sample sizes are also necessary to analyze the differences between TO and TE in regard to the outcome. Furthermore, a randomized, prospective study is also necessary, in which patients are assigned to groups according to their IFN-γ and IL-8 levels in serum. Cutoff values of these cytokines from these studies will then serve as objective criteria for a reliable patient selection undergoing TE/TO.

Conclusion

Higher levels of IL-8 and IFN-γ in serum are associated with less improvement of health-related quality of life after TE or TO in recurrent acute tonsillitis. Thus, these cytokines may serve as preoperative predictors of the patient-related outcome. Tonsillectomy/TO improve QoL in patients having recurrent tonsillitis independent from the number of acute tonsillitis episodes.

Authors' Note

An informed consent has been obtained for any procedure involving the patients described in this article.

Declaration of Conflicting Interests

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ORCID iD

Christoph Spiekermann https://orcid.org/0000-0002-0775-2788

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