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Tonsillotomy for Periodic Fever Syndrome: A Randomized and Controlled Trial

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Objective: Tonsillectomy is an effective treatment for periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome. Tonsillotomy has a milder operative risk profile and postoperative morbidity in children than tonsillectomy. We aimed to compare the efficacy of tonsillotomy to observation-only in children with PFAPA syndrome at a 3-month follow-up.

Methods: This was a randomized multicenter trial with sequential design. Participants were randomized into a tonsillotomy group and a control group that was only observed. The trial started in 1/2017 and was accomplished in 12/2021 with 16 patients (10 boys, six girls, the mean age 4.2 years). The symptoms were monitored with daily symptom diaries.

Results: After the 3-month follow-up, 7/8 patients (87.5%) in the tonsillotomy group and 2/8 (25%) patients in the control group were free from PFAPA symptoms (95% CI 13% to 87%; $p = 0.0021$). The mean number of days with fever was 2.6 (SD 3.7) in the tonsillotomy group and 8.0 (SD 6.5) days in the control group ($n = 8$) ($p = 0.06$). Mean number of fever days compatible with PFAPA syndrome was 0.8 (SD 1.4) in the tonsillotomy group and 6.5 (SD 6.0) in the control group (95%CI −10% to −1%; $p = 0.007$). Rescue tonsillectomy was needed for all patients in the control group and none of the patients in the tonsillotomy group.

Conclusions: Tonsillotomy might be an effective treatment option for children with PFAPA syndrome. Further studies are needed to clarify the long-term efficacy of tonsillotomy for treating PFAPA.

Key Words: children, lymphoid tissue, periodic fever, tonsillotomy, tonsils.

Level of Evidence: 2

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INTRODUCTION

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is the most common periodic fever syndrome among children, affecting about 2.3/10,000 children up to 5 years of age per year.[1–3] The onset of fever occurs mainly in children under the age of 5 years, and the affected children suffer from episodes of high fever every 4 to 5 weeks.[4,5] The syndrome is long lasting and causes significant burden on the patients and their families.[6,7]

The etiology of PFAPA syndrome is unknown but it is considered to be an autoinflammatory disease.[8–10] Unlike monogenic autoinflammatory periodic fever syndromes, PFAPA can be effectively treated by extracapsular tonsillectomy (TE). According to previous data, the efficacy of TE is about 90%.[11–13] Spontaneous healing is possible but usually requires many years.[4,11,14] Glucocorticoids can be used in PFAPA syndrome to shorten the fever flares, but they do not prevent upcoming episodes and may escalate the frequency of the PFAPA flares and cause considerable side effects.[4,5,15,16]

Although TE is effective in PFAPA syndrome, the operation can cause peri- or postoperative hemorrhage and intense postoperative pain lasting for 1–2 weeks. Tonsillotomy (TT) (partial tonsillectomy, intracapsular tonsillectomy, intracapsular tonsillar reduction) has become an option for TE in children with obstructive breathing disorders because of its significantly lower risk of complications and postoperative morbidity.[17–20] TT has not been studied in PFAPA. In a case series, TT was performed in one 15-month-old child with PFAPA with a good result.[1]

In this randomized multicenter sequential trial, we aimed to investigate the clinical efficacy of TT in the treatment of PFAPA syndrome in children as compared to clinical observation-only with no treatment.

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MATERIALS AND METHODS

Study Design and Oversight

We used a randomized, sequential trial design to measure the efficacy of TT compared to observation-only (control group) in children with PFAPA syndrome during 3-month follow-up. In sequential design, the sample size is not fixed, as the trial consists of pre-planned, repeated series of comparisons. Recruitment and comparisons were continued until it was possible to make a decision as to whether one treatment could be regarded as superior to another, or that both treatments are equally effective. Sequential design offers a possibility to find a difference between the treatment groups with the smallest possible sample size. Maximum sample size for pre-planned number of stages was calculated to achieve the pre-specified power and to maintain a specified type I error rate. The protocol of the study was reviewed and found acceptable by The Regional Ethics Committee of the Northern Ostrobothnia Hospital District, Oulu, Finland (EETTMK 50 /2017) and reported in ClinicalTrials.gov (Identifier NCT03331497).

Recruitment

We recruited consecutive PFAPA patients from three Finnish tertiary care pediatric hospitals from November 2017 to December 2021. All the patients were examined by a pediatrician and/or otolaryngologist dedicated to the treatment of PFAPA syndrome. Because of the local practice, glucocorticoids were not used in treating the patients. The inclusion criteria were age under 12 years at the onset of the symptoms and fulfilling the diagnostic criteria for PFAPA syndrome: history of five or more regular fever periods with no other explanations for fevers and asymptomatic interval between fevers and normal growth and development.[21] As we focused the interest of intervention only on palatine tonsils, we excluded all the patients that were suspected to need simultaneous adenotomy. Written, informed consent was obtained from the parents or legal guardians.

Randomization

The recruited patients were randomized either to TT within 1 month from randomization or observation-only for 3 months (control group). The statistician created a computerized randomization list, and numbered opaque envelopes containing a code for the study group were prepared and sealed accordingly. After written informed consent was received, the study doctor opened an envelope revealing the treatment group: TT within 30 days or observation-only during the 3-month follow-up (Fig. 1).

Interventions

In the TT group, the operator estimated the sizes of the tonsils by inspection and palpation, and then at least half of the volume of the palatine tonsils was carefully removed, keeping the tonsillar capsule untouched. Adenoid tonsils were not operated on. The patients were operated on with Coblation® radio frequency ablation equipment (Smith&Nephew plc, Hertfordshire, United Kingdom) using a PROcise® EZ View™ wand.

In the control group, the participants were observed without any treatments.

Clinical Follow-up

The symptoms were monitored with symptom diaries for 3 months after TT (TT group) or randomization (control group). The symptom diary contained daily questions about fever (over 38°C), cough, rhinitis, vomiting, earache, diarrhea, squinting, eating, medication, visits to health care and absence from work/school/ daycare. We chose a 3-month follow-up period to be able to offer rescue tonsillectomy to the control group within a reasonable time. After 3 months follow-up, the parents or legal guardians of the study patients returned the diaries and were interviewed via phone regarding the symptoms. After this 3-month follow-up, conventional tonsillectomy was offered as a treatment in both groups if the symptoms continued. In addition, the participants were contacted by telephone 6 months after the end of diary follow-up, that is, about 9 months after the recruitment (Fig. 1).

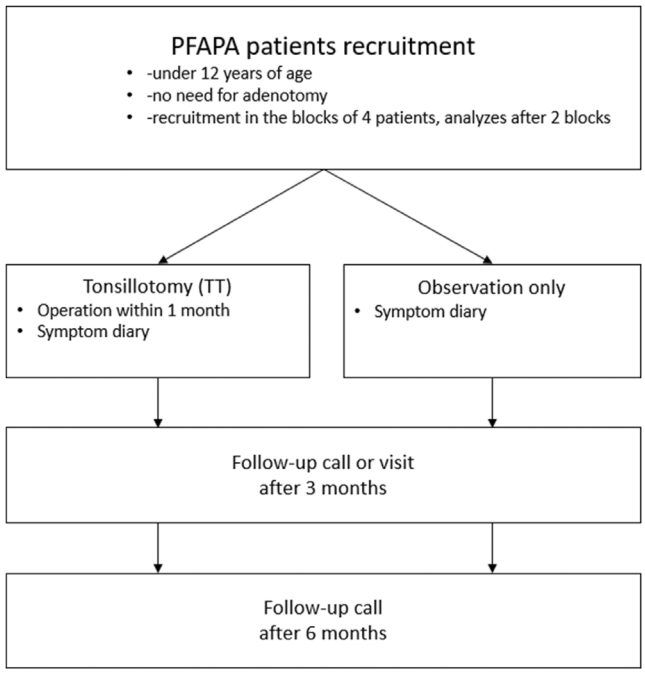

Fig. 1. Recruitment of the patients.

Outcomes

The primary outcome was the proportion of patients without symptoms applicable to PFAPA 3 months after TT or randomization. Secondary outcomes included the number of days with a fever over 38°C in symptom diaries during the 3-month follow-up, the number of febrile days without signs of respiratory or gastrointestinal infections, the proportion of patients without PFAPA symptoms at 9 months, and the proportion of patients needing rescue surgery (TE).

Sample Size Calculation and Statistical Methods

We considered a 40% absolute difference in the proportion of children cured by TT (90%) compared to observation only (50%) as clinically important. We used a two-sided Whitehead design and a maximum likelihood estimation (MLE) boundary scale in sequential design. We chose a type 1 error of 5%, a statistical power of 80%, and five interim analyses. In this sequential study design, the required sample size ranged from 8 to 38 patients. The null hypothesis was that the proportion of patients free from PFAPA symptoms does not differ between the TT and control groups. The study ended when the study boundaries were crossed (null hypothesis rejected) in pre-planned interim analyses or after 38 patients.

We used SAS 9.4 software (SAS Institute Inc., Cary, NC, USA) for sequential trial analyses and SPSS Statistics 27.0

(IBM, Armonk, NY, USA) to perform the statistical analyses for secondary outcomes. We compared the fever days between the patients in the TT and control groups. For continuous variables, we calculated the means (SD) or medians (range) for each group and tested the statistical significance of the differences with either the Student's *t*-test or the Mann–Whitney *U* test according to the distributions. We calculated 95% confidence intervals (95% CI) for the differences between the groups.

Interim Analyses

The first interim analysis was made in March 2020, when eight patients were monitored. The pre-defined boundaries were not crossed, and we continued recruiting. The recruitment was suspended from March to June 2020 because of the COVID-19 pandemic and the lockdown. The second analysis was accomplished in December 2021, when 16 patients had completed monitoring. The pre-defined boundaries were crossed, and the recruitment was ended (Fig. 2).

RESULTS

The study was completed when the pre-defined statistical boundary was crossed after 16 participants had accomplished the 3-month follow-up. The study groups consisted of 10 boys (63%, $n = 16$) and six girls. None of the patients reported regular usage of medication. The mean age at the onset of PFAPA symptoms was 3.4 years (SD 3.2), and it was 4.2 years (SD 3.2) at the time of recruitment. PFAPA fevers were associated with verified symptoms of aphthous stomatitis, adenitis and/or pharyngitis in 15 (93%) patients. One patient in the control group had periodically recurring fever as the only symptom of PFAPA. In the TT group, the mean time from recruitment to operation was 26.5 days (SD 10.5) (Table I).

TABLE I.
Baseline Characteristics of the 16 PFAPA Patients Included the Sequential Analyses.

	Tonsillotomy Group ($n = 8$)	Control Group ($n = 8$)
Sex (male)	4 (50%)	6 (75%)
Age at the onset of the fevers in years (mean, SD)	3.8, 3.8	3.0, 2.7
Age at the time of recruitment in years (mean, SD)	3.9, 3.8	4.5, 2.7
Associated symptoms (aphthous stomatitis, pharyngitis, adenitis)	8 (100%)	7 (87.5%)
Duration of fever flare (mean, days)	3.5	4.2
Duration of PFAPA period (mean, days)	25.6	26.0

Primary Outcome

After the 3-month follow-up period, 7/8 patients (88%) in the TT group and 2/8 (25%) patients in the control group were free from PFAPA symptoms (95% confidence interval of the difference, CI, 12.8–87.2; $p = 0.0021$).

Secondary Outcomes

The mean number of all febrile days was 2.6 (SD 3.7) in the TT group ($n = 8$) and 8.0 (SD 6.5) in the control

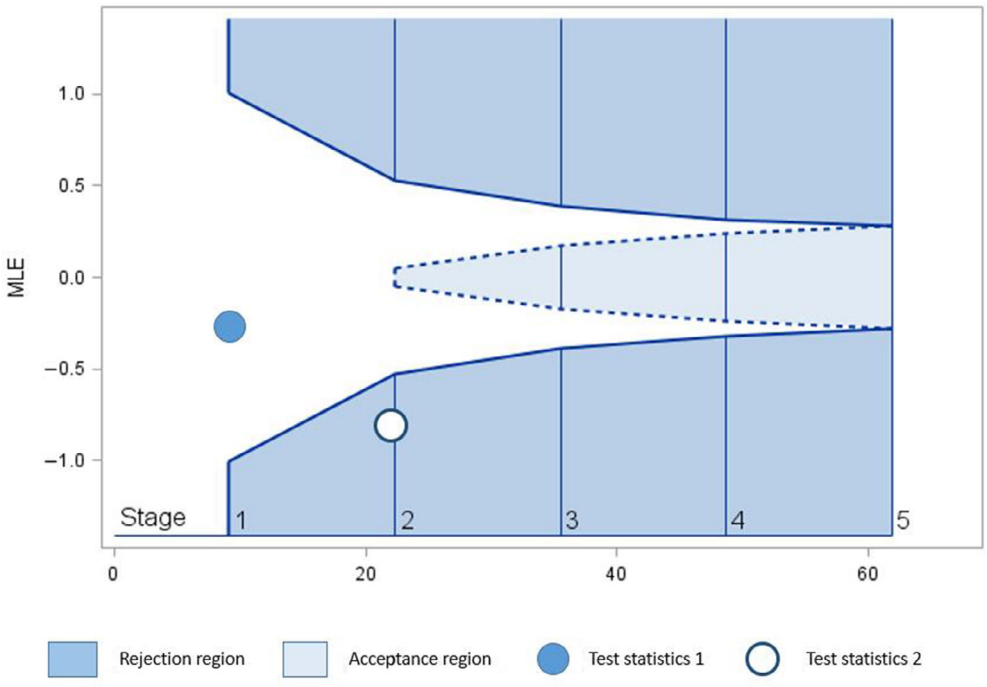

Fig. 2. Blue circle represent the first sequential assessment after the two complete blocks. The test statistics lies in the acceptance region and the null hypothesis is accepted ($p > 0.05$). The trial should be continued. The white circle represent the result of the second assessment after the four complete blocks. The test statistics lie in the rejection region, and the null hypothesis is rejected. The treatment appeared to be effective with a *p*-value <0.05. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

TABLE II.
Primary and Secondary Outcomes in 3-month Follow-up after Tonsillotomy (TT Group) or Recruitment (Control Group).

		Tonsillotomy Group (TT Group) ($n = 8$)	Control Group (Controls) ($n = 8$)	Difference (95% CI)	p Value for the Difference
Primary outcome					
Patients without PFAPA symptoms at 3 months		7 (88%)	2 (25%)	62.5% (12.8 to 87.2)	0.021
Secondary outcomes					
Total number of days with fever	Mean (SD)	2.6 (3.7)	8.0 (6.5)	−5.40 (−11.00 to 0.23)	0.06
	Median (range)	1 (9.0)	6.5 (20.0)		
Febrile days with URTI[a] or gastroenteritis	Mean (SD)	1.9 (3.0)	1.5 (2.1)	0.38 (−2.42 to 3.17)	0.7
	Median (range)	0.5 (8.0)	0.0 (5.0)		
Number of PFAPA related febrile days	Mean (SD)	0.8 (1.4)	6.5 (6.0)	−5.75 (−10.40 to −1.10)	0.007
	Median (range)	0.0 (4–0)	5.0 (20.0)		
Rescue TEs		0	8 (100%)	−100% (−100 to −59.2)	<0.0001
No PFAPA symptoms at the 9 months follow-up call[b]		8 (100%)	8 (100%)		

[a]Upper respiratory tract infections.
[b]Six months after the end of 3-month diary follow-up.

group ($n = 8$) during the 3-month follow-up ($p = 0.06$ of the difference). The mean number of fever days compatible with PFAPA syndrome (febrile days without signs of respiratory or gastrointestinal infections), was 0.8 (SD 1.4 days) in the TT group and 6.5 days (SD 6.0) in the control group (95% CI −10.40 to −1.10; $p = 0.007$ of the difference) (Table II).

Rescue TE was made for none of the patients in the TT group, but for all the patients in the control group. One patient in the TT group reported experiencing 4 days PFAPA flare after TT, but as the symptoms were less severe and the frequency lower than before the operation, the patient was not willing to undergo TE.

All the patients were free from PFAPA symptoms at the time of 9-months follow-up call (6 months after the 3-month diary follow-up). There were no reported complications.

DISCUSSION

In this randomized and controlled sequential trial, TT appared to be effective in ending the symptoms of PFAPA syndrome in children. In previous trials, TE has been shown to be an effective treatment for PFAPA, but the operation is associated with postoperative pain for up to 2 weeks and moderate risk of postoperative complications. According to the present results, less invasive TT may be sufficient for treating PFAPA.

TT is increasingly used in treating disorders caused by hypertrophic tonsils in children, and it has turned to be the most common pediatric palatinal tonsil operation in Nordic countries.[22,23] TT is considered to have a safer risk profile than TE.[24,25] According the Swedish National Tonsil Surgery Register, 0.4% of pediatric patients experience postoperative hemorrhage after TT and severe pain for 2–7 days, whereas after TE, hemorrhage is experienced by 1.2–1.6% of patients, and severe postoperative pain may last for 6–12 days.[17,18] Thus, TT might offer a safer and more comfortable effective treatment option for patients with PFAPA.

PFAPA heavily burdens children and their families.[6,7] The mean duration of the disease is reported to vary from three to 6 years, but also longer durations, up to 24 years, has been reported.[1,4,14] Therefore, it is understandable that in this study, the two patients in the control group who had no PFAPA flares in the 3-month follow up were still willing for the rescue operation to ensure recovery—they were eventually operated on. As PFAPA syndrome frequently and repeatedly affects small children who need constant care, especially when they are feverish, safer and more effective treatments are necessary.

The mechanisms of the effectiveness of tonsil surgery in PFAPA syndrome are not known. It has been suggested that the volume of the removed tonsillar tissue could be crucial in the efficacy of operative treatments in PFAPA syndrome.[26,27] In this trial, the amount of removed tonsillar tissue was often small, adenoids were left untouched, and the effect on PFAPA symptoms was still evident. In addition to the volume of the tonsils, localization of the removed tissue may be important. The microbiome of the tonsils has been suggested to act as an inflammatory stimulus or disease modulator, and biofilms are reported more often on the surfaces of the tonsils than controls.[28–30] It remains unclear whether eliminating the surface of the tonsils or reducing the amount of lymphatic tonsillar tissue is important.

Limitations and Strengths

The main limitation of this study is the rather short follow-up period. Thus, the long-term outcome after TT is not known, based on the present results. The sample size is seemingly small, but because of the chosen statistical method, it actually indicates the superior effectiveness of the treatment in the sequential design model. Although 3 months constitutes a short follow-up period, the rhythm of the fever flares should have appeared, as the mean PFAPA period in both study groups was 26 days. In

addition, all participants were reached by phone after 6 months.

Our design was not blinded, as blinding with sham operations is not easy to organize and justify especially in children. This might have had an effect in collecting the follow up data with symptom diaries. However, the fever flares in PFAPA syndrome are quite substantial and we think that the lack of blinding does not considerably downfall objective measuring of the primary outcomes.

The main strength of this study was its design. Randomization and thorough follow-up without dropouts provided consistent data on the primary outcome. The sequential design enabled us to obtain reliable results with the smallest possible sample size, which is important with respect to these invasive procedures performed on young children.

CONCLUSIONS

To our knowledge, this is the first randomized trial investigating TT in PFAPA patients. As the syndrome heavily burdens children and their families, effective but less invasive treatments are welcome.[6,7] In the present study, TT would appeare to be an effective treatment for children with PFAPA. Thus, the treatment of PFAPA with TT should be considered in clinical practice, as it likely offers a safer and more comfortable operative approach than TE.

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