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Effect of prophylactic amoxicillin on tonsillar bacterial pathogens after (adeno)tonsillectomy in children

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ABSTRACT

Objectives: Unnecessary and inappropriate antibiotic use is an increasing global health challenge. In limited resource settings, prophylactic antibiotics are still often used in (adeno)tonsillectomy (AT), despite evidence against their effectiveness. This study aimed to investigate the effect of prophylactic amoxicillin, given after AT in children.

Methods: This is a secondary analysis from a two-center, double-blinded, randomized controlled, non-inferiority trial to study the effect of prophylactic amoxicillin on post-AT morbidity. Children aged 2-14 years with recurrent chronic tonsillitis and/or obstructive sleep apnea were randomly assigned to receive either placebo or amoxicillin for 5 days after the operation. Pre- and postoperative samples were collected for polymerase chain reaction (PCR) analyses to detect the five most important pathogens known to be common causes of tonsillitis. PCR results were compared before and after surgery as well as between placebo and amoxicillin.

Results: PCR results were obtained, 109 in the amoxicillin group and 115 in the placebo group. In the amoxicillin group, 91% of patients had at least one positive PCR test before surgery and 87% after surgery. In the placebo group, the respective percentages were 92% and 90%. In both groups, a decrease in the total number of pathogens was found after surgery.

Conclusion: Prophylactic amoxicillin given after AT in children did not show a clinically relevant effect with respect to the number of oropharyngeal microorganisms as compared to placebo.

Introduction

In Tanzania, as in many other settings with limited resources, antibiotics are misused and overprescribed [1]. Misuse of antibiotics contributes significantly to the development of antimicrobial resistance (AMR) [2]. AMR has been on the rise and imposes high costs of obtaining superior antibiotics to treat basic infections but also endangers the lives of millions of people living in these settings [3,4].

Children are the most vulnerable population when it comes to antibiotics misuse and overprescription due to several facts. Diarrhea and respiratory infections, such as (adeno)tonsillitis are very common in this population and are often mismanaged with antibiotics, regardless of the etiology [5]. Antibiotics are also widely administered for prophylactic purposes, such as during or after (adeno)tonsillectomy (AT), being the most common pediatric surgical procedure. This happens in many limited resource settings due to limited stewardship, poor understanding of already available guidelines, aberrant local guidelines, or personal opinion of the benefit of these antibiotics for the individual patient [6–11].

Prophylactic antibiotics are prescribed to prevent complications, especially surgical site infections (SSI). The antibiotics utilized should be bactericidal and should target the most common organisms of the SSI. In case of AT those are: *Haemophilus infuenzae, Moraxella catarrhalis, Streptococcus pneumoniae, Staphylococcus aureus,* and *Neisseria meningitidis* [12]. Amoxicillin, among many

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antibiotics, has been one of the most overprescribed and overused essential drugs in Africa [13–17]. In a previous study, we already showed that prophylactic amoxicillin was not effective in preventing or reducing postoperative morbidity, including SSI, in AT patients [18]. However, the question remains if prophylactic antibiotics change the oropharyngeal flora after surgery and thus may help to prevent future episodes of upper airway infections. This study aims to investigate the effect of prophylactic amoxicillin, given after AT in children, on oropharyngeal pathogens as compared to placebo, and to determine if prophylactic antibiotics have any influence, if any effect at all, on the tonsillar flora, as compared to placebo.

Materials and methods

Study population and design

This study describes a secondary analysis of data from a two-center, double-blinded randomized controlled non-inferiority trial performed in Tanzania studying the effect of prophylactic amoxicillin on post-AT morbidity in children with recurrent chronic tonsillitis and/or obstructive sleep apnea due to adenotonsillar hypertrophy. In this trial, all eligible children aged between 2 and 14 years electively scheduled for AT were recruited to participate. Indications for AT were either recurrent tonsillitis as defined as five or more episodes of tonsillitis per year for at least 2 consecutive years and/or obstructive sleep apnea due to adenotonsillar hypertrophy not responding to pharmacotherapy [19]. All ATs were carried out under general anesthesia and with the use of an orotracheal tube. After surgery, participants received either amoxicillin 50 mg/kg body weight or placebo every 8 hours for 5 days as per the trial protocol. Swabs were taken during the study before and after surgery. The results of this randomized controlled trial have previously been published [18].

Ethical approval was received from each participating hospital's ethical committee and the National Institute of Medical Research. Informed consent was obtained from all parents or guardians responsible for the child. The trial was registered in the Pan African Clinical Trials Registry (identifier: PACTR201905466349317) and reported according to CONSORT 2010 guidelines [20].

Sample collection and polymerase chain reaction analysis

Surface tonsillar swabs were obtained intraoperatively and on day 14 postoperative tonsillar fossa swabs were taken for PCR assays using Copan® Universal Transport Media (UTM, COPAN, Brescia, Italy) Collection, Preservation, and Transport System. All swabs were immediately stored at -80°C at the microbiology research lab.

Quantitative PCR (qPCR) for *S. pneumoniae, H. influenzae, M. catarrhalis, S. aureus,* and *N. meningitidis* was performed on all swabs, as previously described [21]. Stored swab samples were thawed on ice and vortexed [21]. From each sample, 100 µl was aliquoted into a 96-well plate. The plate was incubated for 15 minutes at 93°C to lyse the bacteria. The qPCR was performed in six monoplex reactions, using the Bio-rad CFX96 Touch Real-Time PCR Detection System. All reactions were performed in a 10 µl final volume containing 1 µl bacterial lysate, 5 µl SsoAdvanced™ Universal Probes Supermix (Bio-Rad), 400 nM of each primer, and 200 nM probe. Every 96-well plate contained, in duplicate, a no template control and a seven-step tenfold serial dilution of a positive control, starting at approximately 10 ng purified DNA. The qPCR program consisted of 3 minutes of incubation at 95°C followed by 50 cycles of 10 seconds at 95°C and 20 seconds at 60°C. Fluorescence was measured after each cycle. To accurately compare results within targets, the baseline threshold was adjusted so that the positive controls had the same quantification cycle (Cq) value per target for all plates. Cq cutoff was set at 36 for each target.

Table 1
Baseline characteristics.

Characteristics	Study arms	
	Amoxicillin (N = 109) n (%)	Placebo (N = 115) n (%)
Age at surgery(years) (mean [SD])	4.71 (2.28)	5.03 (2.62)
Sex		
Female	55 (51)	47 (41)
Male	54 (49)	68 (59)
Body weight (kg) (mean [SD])	18.7 (5.95)	18.9 (5.86)
Education		
Preschool	55 (51)	59 (51)
Primary	43 (39)	51 (44)
Not enrolled	11 (10)	5 (4)
Residency		
Rural	48 (44)	62 (54)
Urban	61 (56)	53 (46)
Indication		
Recurrent chronic tonsillitis	19 (17.4)	22 (19.1)
Obstructive Sleep Apnea (OSA)	40 (37)	40 (35)
Both	50 (45.9)	53 (46.1)
Brodsky tonsil grading score		
Grade II	4 (3.7)	2 (1.7)
Grade III	53 (48.6)	51 (44.3)
Grade IV	52 (47.7)	62 (53.9)
Previous ear nose throat surgery (yes)	2 (1.8)	4 (3.5)

Statistical analysis

Descriptive statistics were used to summarize the data. The PCR results were compared before and after surgery as well as between placebo and amoxicillin-treated patients. Differences in proportions of positive PCR assays between the placebo and amoxicillin-treated patients were tested using z-tests. Multinomial regression was performed to test the difference between the number of detected postoperative pathogens in the placebo and amoxicillin-treated patients adjusted for the number of detected preoperative pathogens. McNemar's tests were used to compare within-group differences between preoperative and postoperative pathogen counts. Statistical analyses were performed using R (version 4.2.0; R Foundation for Statistical Computing, Vienna, Austria). A *P*-value of less than 0.05 was considered statistically significant.

Results

During the study period, 720 ATs were performed in two hospitals in Northern Tanzania, and 270 children were enrolled in the randomized controlled trial. Swab results were available for 224 patients, 109 in the amoxicillin group and 115 in the placebo group. Baseline characteristics of the trial participants with available swab results are shown in Table 1.

Most participants had positive swabs for one or more bacterial pathogens. In the amoxicillin group, 91% had one or more pathogens detected before surgery and 87% had one or more pathogens detected after surgery, whereas in the placebo arm, this was 92% and 90%, respectively (Table 2). Overall, fewer positive PCR assays were found postoperative as compared to preoperative (42% preoperative vs 32% postoperative [$P = 0.001$] and 38% preoperative vs 26% postoperative [$P < 0.001$] for placebo and amoxicillin group, respectively). However, no difference in the decrease of preoperative and postoperative numbers of positive PCR assays was found between the placebo and amoxicillin group (9% vs 13%; $P = 0.08$, respectively).

Table 2
Number of pathogens detected.

Number of pathogens detected	Amoxicillin (n [%])		Placebo (n [%])		Difference[a] (95% confidence interval)	*P*-value
	Before surgery	After surgery	Before surgery	After surgery		
0	10 (9)	14 (13)	9 (8)	11 (10)	-2.8% (-11.1 – 5.5)	0.51
1	27 (25)	60 (55)	23 (20)	49 (43)	-11.3% (-24.5 – 1.8)	0.09
2	39 (36)	26 (24)	39 (34)	35 (30)	7.3% (-4.5 – 19.0)	0.23
3	28 (26)	9 (8)	38 (33)	14 (12)	4.2% (-3.9 – 12.2)	0.31
4	5 (5)	0 (0)	6 (5)	6 (5)	2.7% (-0.9 – 6.2)	0.14

[a] Difference in number of detected postoperative pathogens between placebo and amoxicillin groups (placebo-amoxicillin) adjusted for the number of detected preoperative pathogens estimated using multinomial regression.

Table 3
Preoperative versus postoperative pathogens in the amoxicillin group.

Pathogen	Preoperative only n (%)	Postoperative only n (%)	Pre and postoperative n (%)	Total n (%)	McNemar's *P*-value
(a)					
H. influenzae	45 (41.3)	14 (12.8)	15 (13.8)	74 (67.9)	<0.001
M. catarrhalis	4 (3.7)	2 (1.8)	0 (0.0)	6 (5.5)	0.68
N. meningitidis	15 (13.8)	14 (12.8)	75 (68.8)	104 (95.4)	1.00
S. pneumoniae	28 (25.7)	6 (5.5)	8 (7.3)	42 (38.5)	<0.001
S. aureus	17 (15.6)	3 (2.8)	2 (1.8)	22 (20.2)	0.004
(b)					
H. influenzae	41 (35.7)	9 (7.8)	36 (31.3)	86 (74.8)	<0.001
M. catarrhalis	5 (4.4)	8 (7.0)	1 (0.9)	14 (12.2)	0.58
N. meningitidis	12 (10.4)	14 (12.2)	84 (73.0)	110 (95.7)	0.84
S. pneumoniae	35 (30.4)	6 (5.2)	15 (13.0)	56 (48.7)	<0.001
S. aureus	8 (7.0)	10 (8.7)	2 (1.7)	20 (17.4)	0.81

Regarding the specific pathogens for both amoxicillin and placebo arms, a high number of PCR were positive for *N. meningitidis,* 95.4% and 95.7%, respectively, followed by *H. influenzae* with 67.9% and 74.8%, respectively (Tables 3a and b).

After surgery, a statistically significant decrease in colonization with *H. influenzae* and *S. pneumoniae* was found in both groups (Table 3a and b). The presence of *M. catarrhalis* and *N. meningitidis* did not change significantly after surgery in both groups. In the placebo group, the number of positive *S. aureus* did not change after surgery, but in the amoxicillin group, a significant reduction in *S. aureus* was observed after surgery. Regarding the individual patients, we found that in some patients, different pathogens combinations were found preoperatively as compared to after surgery in both groups. However, again no differences were found between the placebo group and the amoxicillin group. (See supplementary file: Tables S1a-b and S2a-b)

Discussion

The present study is the first study to investigate the effect of prophylactic amoxicillin on oropharyngeal pathogens after AT. This study shows that tonsillar flora does change after surgery. In some patients, some pathogens are not found anymore after surgery, whereas in others, pathogens are found after surgery that was not there before.

Normal oropharyngeal flora contains different bacteria that can cause (adeno)tonsillitis which in turn causes or worsens obstructive sleep apnea, especially in children. In case of recurrent (adeno)tonsillitis or chronic obstructive sleep apnea, the adenoid and tonsils are often removed. This makes AT one of the most common surgical procedures in children worldwide. In many parts of the world, prophylactic antibiotics are administered during or after AT despite the evidence against their effectiveness. This inappropriate use of prophylactic antibiotics is still widespread in Tanzania, as well as in many other countries, and is considered one of the major contributors to AMR [4,22–25].

However, prophylactic amoxicillin, administered for 5 days after surgery, did not have any effect on these changes in recolonization on the tonsil fossa as compared to placebo except for *S. aureus* which showed a slight decrease. Lower numbers of *H. influenzae* and *S. pneumoniae* were found after surgery in both groups, but the number of *M. catarrhalis* and *N. meningitidis* returned to preoperative levels 2 weeks after AT. This is in accordance with results from a large review study by Brietzke [26]. Whether the lower number of *S. aureus* in the amoxicillin group in this study is a permanent effect remains unknown. Previous studies showed that there is a tendency for fast recolonization of the tonsils and/or oropharynx with oropharyngeal pathogens after treatment with antibiotics [15,27]. The same is found for all pathogens but *S. aureus* in this study. Although this recolonization occurs fast, the rate is not equal for all pathogens. Whether amoxicillin will prevent *S. aureus* from recolonizing the tonsil fossa or whether the recolonization is only slowed down by the antibiotic remains unclear.

Because we used PCR targeting only five pathogens instead of culturing, a less selective method, we may have missed certain pathogens. In contrast, these five bacterial species are the most prominent pathogens identified in the upper respiratory tract [12]. Furthermore, the advantage of using PCR instead of culture is the much higher sensitivity of PCR [28]. An important strength of this study is the high number of participants with diverse social demographic characteristics; unlike most other studies on tonsillar flora and use of antibiotics that were conducted with lower number of participants in socio-demographically more homogeneous populations.

Understanding the side effects, cost, availability of antibiotics, and their contribution toward AMR, the present study provides sufficient evidence that antibiotics are neither appropriate nor necessary as prophylactics in pediatric patients undergoing AT [18]. This even accounts for a limited resource setting such as Tanzania where prophylactic antibiotics are given even more frequently because of poorer hygienic circumstances during surgery. As a global threat, AMR is estimated to rise if no effective measures are taken, especially in resource-limited settings. Surgically, these antimicro-

bial agents have been widely misused, abused, and prescribed without thorough clinical judgment. Findings from this study will contribute to both local and global strategic approaches to addressing and combating antimicrobial misuse, with emphasis on surgical prophylaxis, particularly in pediatric surgeries. This study highlights the need for future clinical trials on the effects of prophylactic antibiotics in other surgeries, addressing the necessity, appropriateness, and financial implications of antibiotic use.

Conclusion

Prophylactic antibiotics do not affect tonsillar recolonization with different bacterial pathogens as compared to placebo after AT and are therefore not advised for that purpose. In addition, not giving amoxicillin will protect against its side effects which might be severe.

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Ethical approval

This study was approved by the Kilimanjaro Christian Medical College Research Ethics and Review Committee (CRERC) and the Tanzanian National Institute for Medical Research (NIMR). Written informed consent will be obtained from the parents/caretakers of each participant.

Author contributions

DK, MR, and NvH designed the study and drafted the manuscript. GH analyzed the data. All authors verified the data and analysis. DK performed inclusion and follow-up of all patients and participates in surgical procedures. DC participated in surgical procedures. CG and MJ were responsible for PCR testing. All authors have read and approved the final version of the manuscript.

Data sharing

The study data are held at Kilimanjaro Christian Medical University College (Kilimanjaro, Tanzania) Department of Otorhinolaryngology. Data access is consistent with both local and national clinical research ethical committee approvals. All requests for data are considered and can be initiated by contacting katundu101@gmail.com.

Declarations competing of interest

The authors have no competing interests to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.04.409.

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