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Bacteriology of Adenoids in Children with Adenoid Hypertrophy despite Mometasone Furoate Administration

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Abstract

Introduction: Topical nasal corticosteroids have been reported to be an effective nonsurgical alternative treatment to control nasal symptoms related to adenoid hypertrophy, but not in all patients. The current study investigates the bacteriology of adenoids in children with non-reduced adenoid size despite mometasone furoate (MMF) administration.

Methods: The patients were randomly divided into two groups: the MMF-administered group and the non-MMF administered group (N-MMFA) afterwards, the MMF-administered group was classified into subgroups according to endoscopic grading as reduced and non-reduced adenoid size. N-MMFA and MMF-administered with non-reduced adenoid size groups (MMF-A/N-RAS) underwent adenoidectomy and the deep bacterial flora of adenoid core specimens taken from these patients were cultured.

Results: No significant differences were detected in terms of the mean number of organisms isolated per patient in MMF-administered but non-reduced adenoid size group and non-MMF administered group. On the other hand, the variety of bacterial species was decreased in MMF-administered but non-reduced adenoid size group when compared to non-MMF administered group. The study groups did not differ in the occurrence of semi quantitative growth. This study demonstrates that MMF has no significant effect on reducing the bacterial load of adenoids in children with MMF-A/N-RAS.

Keywords: Adenoid; Adenoid hypertrophy; Bacterial flora; Mometasone furoate

Introduction

The adenoids, which are lobulated masses of lymphoid tissue located at the back of the nasopharynx, play an important role in both cellular and humoral immunity [1]. Although adenoidal hypertrophy (AH) is one of the most common indications for surgery in the pediatric population, several trials have reported the benefits of intranasal steroid use [2].

In healthy children, the adenoid core contains a polymicrobial flora that can be also a source of polymicrobial pathogens that have a role in the development of infectious diseases according to the alteration of host defense system [3]. Alpha-hemolytic streptococci, coagulase negative staphylococci, *Staphylococcus aureus*, Beta-hemolytic streptococci, *Moraxella catarrhalis*, and *Haemophilus spp*, were accepted as the predominant aerobic bacteria; additionnaly, *Prevotella* spp., *Bacteroides fragilis*, *Fusobacterium* spp, anaerobic gram-positive cocci and *Veillonella parvula* were accepted as the predominant anaerobic bacteria of the adenoid flora [4]. Therefore, the adenoids are considered critically an important bacterial reservoir in children [5].

Mometasone furoate (MMF) is a potent 17-heterocyclic corticosteroid formulated in an aqueous suspension which has a high binding affinity for glucocorticoid receptors [6]. It is administered as an intranasal spray using a manual, metered-dose pump. MMF nasal spray is safe and effective in children, as shown by the 1 year treatment results in children with perennial allergic rhinitis [7]. The effect of MMF on the nasopharyngeal flora as well as its *in vitro* antibacterial activity have been demonstrated [8,9] but its effect on the bacterial load of adenoids has not been elucidated; although it is well known that MMF could reduce the size of adenoids by several mechanisms.

The current study investigates the bacteriology of adenoids in children with non-reduced adenoid size despite MMF administration.

Materials and Methods

The study enrolled 133 children admitted to the Department of Otorhinolaryngology at Taksim Education and Research Hospital with symptoms of nasal obstruction and AH confirmed by fiber optic nasoendoscopy. The exclusion criteria included use of topical or systemic corticosteroid, antihistamine or antibiotics for at least two months at first consultation; viral or bacterial active upper airway infections at the previous month; history of immunodeficiency, chronic infection (including otitis media and sinusitis); patients with severe nasal septal deviation, nasal polyps, choanal atresia, large masses; allergic and non-allergic, non-infectious rhinitis, known allergy to mometasone furoate nasal spray and systemic diseases, such as cystic fibrosis or craniofacial malformation. Five children were secondarily excluded from the study due to the lack of 8 week follow-up data after MMF treatment. The parents of other five children rejected the adenoidectomy procedure. The culture plates of three additional children were not favorable for microbiological evaluation due to an unexpected mold contamination.

This study was approved by our local institutional review board, and written informed consent was obtained from all of the patients' parents.

In this study, a validated endoscopic grading system (ranging from 1 to 4) of adenoid size for fiberoptic nasoendoscopy was used [10]. The endoscopic grading system used for assessing adenoid size has been based on the relationship of the adenoids to adjacent structures (torus tubaris-Eustachian tube orifice, vomer-posterior nasal septum and soft palate) when the patient is at rest. Grade 1 adenoids are nonobstructive and do not contact any of the previously mentioned anatomic subsites. Subsequently, grade 2, 3 and 4 adenoids contact the torus tubaris, vomer, and soft palate (at rest) respectively. Patients with an adenoid size of grade 3 or 4 were enrolled in the prospective study. All endoscopic examinations were performed using a flexible endoscope with an HD camera (Richard Wolf GmbH, Knittlingen, Germany). Both endoscopic examination and grading was performed by the same person (first author) so that examiner has had a clear view of the adenoid tissue because of performing of the endoscopy by himself. The endoscopic size assessment was validated and there was consistency of the adenoid sizing assessment. The patients were unequally randomized (2:1) into two groups: the MMF-administered group (n:80) and the non-MMF administered group (N-MMFA) (n: 40). MMF nasal spray was administered for 8 weeks (50 µg/actuation in each nostril once daily; total daily dose of 100 µg) to 80 patients who will form the MMF-administered group. N-MMFA group received a placebo saline solution during this same period. Patients were endoscopically scored after the completion of treatment, and those showing significant reduction in adenoid size (grade 1 or 2) were considered to belong to the reduced adenoid size subgroup (n=60). The others showed no significant reduction in endoscopic grading (grade 3 or 4) after MMF administration and were considered to belong to the MMF non-reduced adenoid size group (MMF-A/N-RAS) (n=20) and both N-MMFA and MMF-A/N-RAS groups underwent adenoidectomy as soon as possible after planning the operation date. The MMF-administered group with reduced adenoid size were not planned to operate due to ethical concerns. The symptoms of the children in the MMF-administered group were clinically scored for nasal obstruction with a questionnaire before and after 8 weeks of MMF treatment. The intensity of symptoms was scored as 0 (absent), 1 (occasional), 2 (frequent) or 3 (daytime and nighttime symptoms) to assess the degree of nasal obstruction, rhinorrhea, cough, snoring and/or obstructive sleep apnoea [11]. All scores were summed to obtain an overall symptom score for each patient.

The specimen collection was performed by previously described techniques [12]. Adenoid tissue samples were placed in a sterile petri dish after adenoidectomy and the outer tissue was cauterized with a heated scalpel in the operating room. The tissue samples were immediately transported to the microbiology laboratory of the Medical Microbiology Department of Cerrahpasa Medical Faculty in a Carry and Blair transport medium under sterile conditions. In the lab, in a laminar flow cabinet, the adenoid tissue was held by forceps and incised with a sterile scalpel blade on the cauterized surface. Each adenoid core was cut into small pieces and for the isolation of facultative anaerobic bacteria, a portion was inoculated first onto a chocolate agar then onto a blood agar and Mac Conkey agar by a quadrant streak method and was incubated 24-48 h at 37°C. Each different colony types grown on chocolate agar were Gram stained and the *semiquantitative* assessments of *bacterial* growth was determined. Facultative anaerobic bacteria were identified according to standard microbiologic isolation and identification procedures [13]. For the isolation of obligate anaerobic bacteria, small adenoid pieces were inoculated on phenylethyl alcohol anaerobic blood agar, kanamycin and vancomycin anaerobic blood agar, and *Bacteroides* bile esculin agar. Anaerobic conditions were established using Anaero-Gen (Mitsubishi Gas Chemical America, Inc., New York, NY, USA). Anaerobic incubation was performed in anaerobic jars (Oxoid, Columbia, MD, U.S.A.) at 37°C for at least 72 hrs [14,15]. Following incubation, the primary anaerobic plates were examined, all of the different colony types grown in different anaerobe agars were described, Gram stained, and sub cultured to a chocolate medium and a phenylethyl alcohol blood agar to verify the facultative anaerobic or aerotolerant character of the colony and to obtain a pure culture. Additionally a semi quantitative assessment of the growth of these colonies was performed. All obligate anaerobic bacteria were identified using Vitek Anaerobe Identification (ANI) cards (bioMérieux SA, Marcy l'Étoile, France) [14-16].

The semiquantitative determination of growth was described as 1^+, 2^+, 3^+ or 4^+ based on the number of quadrants in which growth appeared. Fewer than 10 colonies in the first quadrant of the agar plate were accepted as 1^+ growth. More than 10 colonies in the first quadrant and fewer than 10 colonies in the second quadrant of the agar plate were accepted as 2^+ growths. The presence of more than 10 colonies in the second quadrant and fewer than 10 colonies in the third quadrant was accepted as 3^+ growths. The presence of more than 10 colonies in the third quadrant and the presence of growth in the fourth quadrant were accepted as 4^+ growths [13].

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Statistical analysis

The data were analyzed with the "Statistical Package for the Social Sciences" (SPSS 20.0) using chi-square test, Fischer's exact test, Mann-Whitney *U-test* and Wilcoxon test. A *p-value* <0.05 was considered statistically significant.

Results

The baseline characteristics of the children are shown in Table 1. There was no significant difference (p>0.05) in age, gender or endoscopic grade between N-MMFA and MMFA groups (Table 1).

Clinical symptom scoring

Although there was a significant decrease in clinical symptom score after MMF administration both in the reduced adenoid size and the non-reduced adenoid size subgroups (p<0.05), the difference between the clinical symptom score before and after MMF administration was higher in children with reduced adenoid sizes (p<0.05) (Table 2).

Endoscopic grading

After MMF administration, the size of the adenoids was significantly decreased to grade 1 and 2 (p<0.05) in the reduced adenoid size subgroup, but, in the non-reduced adenoid size subgroup, the size of the adenoids were grade 3 and grade 4 (Table 2).

Facultative anaerobic and obligate anaerobic bacterial growth

In the series as a whole (n=60), 216 bacterial strains of 20 different species were isolated from the adenoid core specimens (average, 3.60 isolates per adenoid). The most common facultative anaerobic isolates were *coagulase-negative staphylococci, α-hemolytic streptococci, Neisseria spp*. and *Moraxella spp*.

similarly in N-MMFA and MMF-A/N-RAS. On the other hand, *Propionibacterium acnes, Bacteroides fragilis* and *Peptostreptococcus spp*. were the most commonly isolated obligate anaerobic species both in N-MMFA and MMF-A/N-RAS, whereas *Veillonella parvula* which was isolated from N-MMFA was not found in MMF-A/N-RAS. Although there was not a statistically significant difference in terms of the total facultative and obligate anaerobic isolates number per patient between N-MMFA (2.10 and 1.43, respectively) and MMF-A/N-RAS (1.85 and 1.63, respectively) groups, there was a decline in the species variety of isolated organisms in the non-reduced adenoid size subgroup (20 *vs.* 13, respectively) [12].

The study subgroups did not differ in term of 3^+ and 4^+ growths (Tables 3 and 4).

Table 1: Baseline characteristics (age, sex, and endoscopic grade) of the study patients; *All data are presented as the number (%); **p<0.05 was considered statistically significant.

	Non-MMF administered group	MMF-administered group	p**
Age (mean ± SD)	7.3 ± 2.5	7.2 ± 2.1	0.844
Sex	21(52.5)	42(52.5)	0.985
***Male**	31(77.5)	62(77.5)	0.997
Grade	9(22.5)	18(22.5)	

Table 2: Clinical symptom score and endoscopic grade of the subgroups of MMF-administered group before and after MMF administration; **p<0.05 was considered statistically significant.

	MMF-administered group		
	Non-reduced adenoid size	Reduced adenoid size	p**
Clinical symptom score before MMF administration (mean ± SD)	8.00 ± 1.45	6.24 ± 1.32	0.000
Clinical symptom score after MMF administration (mean ± SD)	7.35 ± 1.42	3.46 ± 0.98	0.000
Difference before and after MMF administration (mean ± SD)	0.65 ± 0.98	2.78 ± 1.06	0.000
Endoscopic grade before MMF administration*			
Grade 3	12(60)	50(84)	0.073
Grade 4	8(40)	10(16)	
Endoscopic grade after MMF administration*	0(0)	4(7)	0.000
Grade 1	0(0)	56(93)	
Grade 2	15(75)	0(0)	
Grade 3	5(25)	0(0)	
Grade 4			

Table 3: Facultative anaerobic and obligate anaerobic bacteria isolated from the core of excised adenoids; N-MMFA: Non-Mometasone Furoate administrated, MMF-A/N-RAS: Mometasone Furoate-Administered with Non-Reduced Adenoid Size; *p<0.05 was considered statistically significant.

Number of isolates in the adenoids			
	N-MMF A	**MMF-A N-RAS**	**p****
Facultative anaerobes			
Diphtheroid bacilli	10	2	0.304
Methicillin-sensitive *Staphylococcus aureus (MSSA)*	7	3	-

Coagulase-negative staphylococci	22	10	0.714
α-Hemolytic streptococci	18	12	0.273
β-Hemolytic streptococci	2	1	-
Streptococcus pneumoniae	1	-	-
Neisseria spp.	12	5	0.685
Moraxella spp.	10	4	0.756
Haemophilus parainfluenzae	4	-	0.291
Obligate anaerobes	-	-	-
Propionibacterium acnes	23	11	0,854
Fusobacterium nucleatum	3	2	-
Bacteroides fragilis	11	7	0,550
Porphyromonas asaccharolytica	1	-	-
Prevotella melaninogenica	5	-	0,159
Prevotella buccae	2	2	-
Porphyromonas gingivalis	2	-	0,548
Peptostreptococcus spp.	8	4	-
Peptostreptococcus anaerobius	1	2	0.255
Finegoldia magna	1	0	-
Veillonella parvula	8	-	0.043
Total isolates	151	65	

Table 4: Number of facultative anaerobic and obligate anaerobic bacteria determined according to the semi- quantitative evaluation of growth in N-MMFA and MMF-A/N-RAS; Numbers in brackets denote the mean number of organisms isolated per patient ± SD.

	N-MMFA		MMF-A/N-RAS	
	(1+) – (4+)	(3+) – (4+)	(1+) – (4+)	(3+) – (4+)
Facultative Anaerobe	86 (2.1±0.66)	37(0.93±0.47)	37(1.85±0.59)	20(1.0±0.69)
Obligate Anaerobe	65(1.63±0.59)	26(0.65±0.23)	28(1.40±0.88)	17(0.85±0.35)
Total bacteria	151(3.78±0.86)	63(1.58±0.93)	65(3.25±0.97)	37(1.85±0.99)

Discussion

A recent study by Aksoy et al. [8] indicated that mometasone furoate could increase the colonization of the potential pathogens in some of the patients at the subclinical level particularly in the nasopharyngeal area. The mechanism by which steroids could reduce nasal airway obstruction is unclear. One of the proposals is lympholytic action of steroids causing a direct reduction in size; another effect may be a reduction in adenoidal and nasopharyngeal inflammation via anti-inflammatory effect of steroids. The last hypothesis is recommended as a reduction in the role of adenoids as a reservoir for infection [17].

In the present study we found 75% of children have revealed symptoms with significant reduction in adenoid size. However, 25% of children have improved clinical symptom scores with no reduction in adenoid size despite MMF administration. This might be partly explained by the anti-inflammatory effect of nasal steroids without a lympholitic action causing a direct reduction in adenoid size. We recommended that anti-inflammatory property of steroids is prior in these patients. Our data were also supported by Cengel [18] and Berluchi [19] Berluchi reported 77.7% of reduction in adenoid size in MMF-A whereas this ratio is 50% in the study of Cengel et al.

The colonization of both commensal and potentially pathogenic facultative and obligatory anaerobes was decreased and some of the species were not isolated in MMF-A/N-RAS. This might be partly explained that, MMF does not evidently exert a significant effect on the reduction of bacterial load in adenoids of those children which serve as reservoirs for infections [20-22].

On the other hand, the improvement in clinical scoring without a sufficient reduction in adenoid size in this study may be explained by the anti-inflammatory effect of the steroids on the nasal mucosa and turbinates rather than a lympholitic effect on the adenoids inducing a direct reduction in size. The mechanism of the antimicrobial action of nasal steroids still remains unclear. Repeated applications of the spray may be needed to exert antibacterial activity in vivo.

One of the limitations of this study is that MMF-A/N-RAS was not characterized in respect to chronic or recurrent infection course. These are therefore, preliminary results.

The predominant facultative and obligate anaerobes in the present study were similar both in the in NMMF-A and MMF-A/N-RAS. Recent studies [23-25] have been reported on the aerobic and anaerobic bacteriology of the adenoids of children with adenoid hypertrophy and similar predominant species were found. It appears evident that even if MMF administration leads to a decrease in the total number of isolated bacteria, this may not be accomplished in children with non-reduced adenoid sizes to ensure a significant inhibition of bacterial growth in adenoids that serve as reservoirs for infections.

One of the interesting points of the present study is that, non-pathogenic *V. parvula*, which might have an effect on the antimicrobial resistance in the presence of multispecies biofilms [26], was not isolated in MMF-A/N-RAS. Growing in a biofilm together with a non-pathogenic bacterium like *V. parvula* changes the physiology of some species giving an advantage to survive despite antimicrobial therapy. On the other hand *P. acnes* and methicilline-sensitive *S. aureus* are the main bacteria that are involved in biofilm formation. In the present study the number of isolated both of this bacterium was decreased after MMF administration despite of no reduction in adenoid size. *B. fragilis* and *F. nucleatum* have potent virulence factors and occasionaly enfect organisms. *F. nucleatum* is believed to contribute to the coaggregation of polymicrobial oral bacteria, leading to biofilm formation in plaque and periodontal disease

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[27]. Recently it has been also assumed that *P. melaninogenica* might be involved in biofilm formation. Biofilms of pathogenic bacteria may contribute to the persistence of pathogens. Controlled studies indicate that adenoidectomy is effective in the treatment of chronic otitis media, suggesting that the adenoids may act as a reservoir for pathogens. Although, MMF does not seem to lead a significant reduction in the role of adenoids as reservoir for infections, we can assume that MMF may probably prevent the growth of some potential pathogens in a biofilm together with non-pathogenic bacteria which may be important in the bacterial susceptibility to antimicrobials. This effect might partly explain the decline of bacterial growth in MMF-A/N-RAS. Understanding that chronic bacterial infections are biofilm related, this leads to development of rationale strategies for treatment [28].

In the present study we also made semi-quantitative cultural growth as studied by Stjernquist-Desatnik et al. [29]. Although we found no significant semi quantitative differences between the subgroups in the patients with adenoid hypertrophy, we might assume that the percentage of semi quantitative growth of 3^{+}-4^{+} to 1-4^{+} was elevated after the administration of MMF despite of no reduction in adenoid size. This may be explained by the assumption that the continuous administration of MMF-A may have a modulatory effect on alteration of adenoid bacterial colonization which contributes to the growth of bacteria towards a 3^{+}-4^{+} densities.

In conclusion, the administration of nasal steroids in children with adenoid hypertrophy as a first-line approach may significantly improve nasal obstruction symptoms, but does not always achieve an adequate reduction in adenoid size. A longer follow-up study should be planned to determine the frequency of recurrent infections in those children with non-reduced adenoid sizes despite MMF administration in consideration of the role of MMF on the adenoid microbial flora and potential pathogens.

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