ORIGINAL ARTICLE

Fatih Alper Akcan[1]
Hümeyra Bayram Akcan[2]
Yusuf Dundar[3]
Ahmet Uluat[4]
Esra Karakuş[5]

[1] Düzce University School Of Medicine, Department of Otolaryngology, Düzce, TURKEY
[2]Ministry of Health, Atatürk Hospital, Department ofInternal Medicine, Düzce, TURKEY
[3]Rize Government Hospital, Department of Otolaryngology, Rize, TURKEY
[4]Ministry of Health, Evliya Çelebi Training and Research Hospital, Department of Otolaryngology, Kütahya, TURKEY
[5]Ankara Children's Hematology and Oncology Training and Research Hospital, Pathology Department, Ankara, TURKEY

Corresponding Author:
Fatih Alper Akcan
Düzce University School of Medicine, Department of Otorhinolaryngology, Duzce , Turkey
Tel:+90 505 767 11 13
E-mail: f.akcan@yahoo.com

Received: 14.12.2017
Acceptance: 06.07.2018
DOI: 10.18521/ktd.365710

Konuralp Medical Journal
e-ISSN1309–3878
konuralptipdergi@duzce.edu.tr
konuralptipdergisi@gmail.com
www.konuralptipdergi.duzce.edu.tr

The Histopathological Findings of Adenoid Tissue After Topical Mometasone Furoate Implementation

ABSTRACT

Objective: Pediatric sleep disordered breathing (SDB) is a common childhood disease with a potential risk of several comorbidities. The most common cause of SDB in childhood is upper airway obstruction due to adenotonsillar hypertrophy and the classical treatment is adenotonsillectomy. However, it carries a risk of many complications and persistent apnea. Topical nasal steroid treatment may be an alternative to surgery in the treatment of pediatric SDB. However, histopathological effects of topical nasal steroids are mostly understudied.

Methods: A retrospective controlled clinical study in an academic tertiary referral center. A total of 110 children were involved in the study who underwent adenoidectomy for the treatment of SDB. The study group (51-children) was treated with topical nasal mometasone furoate monohydrate 100 mcg/day. The control group (59-children) was selected randomly and all had no history of topical nasal steroid pre-operatively. Post-operative adenoidectomy specimens were reviewed according to acute/chronic inflammation findings, follicular hyperplasia, goblet cell hyperplasia, squamous metaplasia, fibrosis, atrophy, ulcer and hemorrhage. The findings were scored semiquantitatively for statistical analysis.

Results: Chronic inflammation findings, follicular hyperplasia and goblet cell hyperplasia were significantly decreased in the study group in addition fibrosis, atrophy and ulcer findings were significantly increased in the study group. However, there was no statistical difference between the groups according to acute inflammation and hemorrhage.

Conclusions: Topical nasal corticosteroids significantly suppress the nasopharyngeal inflammatory process in SDB. This treatment may be an alternative to surgery at least in patients with mild and moderate disease.

Keywords: Sleep Disordered Breathing, Adenotonsillectomy, Nasal Corticosteroid, Histopathology

Topikal Mometazon Furoat Kullanımının Adenoid Doku Üzerindeki Histopatolojik Etkisi

ÖZET

Amaç: Uykuda solunum bozukluğu (USB), birçok komorbidite riski taşıyan yaygın bir çocukluk çağı hastalığıdır. Çocukluk çağında USB'nun en sık görülen nedeni adenotonsiller hipertrofiye bağlı üst solunum yolu tıkanıklığıdır ve klasik tedavi adenotonsillektomidir. Bununla birlikte, birçok komplikasyon ve persistan apne riski taşır. Pediatrik USB tedavisinde topikal nazal steroid tedavisi cerrahiye alternatif olabilir. Bununla birlikte, topikal nasal steroidlerin histopatolojik etkileri yeterince anlaşılamamıştır.

Gereç ve Yöntem: Çalışma üçüncü basamak bir sağlık merkezinde verilerin retrospektif olarak taranması şeklinde planlanmıştır. Çalışmaya USB nedeni ile adenoidektomi uygulanan toplam 110 çocuk dahil edildi. Çalışma grubuna 51 çocuk, topikal mometazon furoat monohidrat 100 mcg/gün ile tedavi edilmişti. Kontrol grubu (59 çocuk) rasgele seçildi ve preoperatif olarak topikal nasal steroid öyküsü yoktu. Ameliyat sonrası adenoidektomi örnekleri, akut/kronik inflamasyon bulguları, foliküler hiperplazi, goblet hücre hiperplazisi, skuamoz metaplazi, fibrozis, atrofi, ülser ve kanamaya göre gözden geçirildi. Bulgular istatistiksel analiz için semikantitatif olarak değerlendirildi.

Bulgular: Çalışma grubunda kronik inflamasyon bulguları, foliküler hiperplazi ve goblet hücre hiperplazisi anlamlı olarak azalırken, fibrozis, atrofi ve ülser bulguları anlamlı olarak arttı. Bununla birlikte akut enflamasyon ve kanama açısından gruplar arasında istatistiksel olarak bir fark yoktu.

Sonuç: Topikal nazal kortikosteroidler USB'de nazofaringeal inflamatuvar süreci önemli derecede bastırmaktadır. Bu tedavi, en azından hafif ve orta şiddette USB olan hastalarda cerrahiye alternatif olabilir.

Anahtar Kelimeler: Uykuda Solunum Bozukluğu, Adenotonsillektomi, Nazal Kortikosteroid, Histopatoloji

INTRODUCTION

Sleep disordered breathing (SDB) is one of the most common childhood disorders with a range from simple snoring to obstructive sleep apnea (OSA) (1). The mildest form of SDB is "primary snoring" which refers to snoring without apnea and frequent arousal from sleep (2). The moderate form of SDB is "upper airway resistance syndrome" that refers to snoring, increased breathing effort during sleep, sleep disturbance and daytime sleepiness without obvious apnea (1,2). The most severe form of SDB is "obstructive sleep apnea" which is characterized by snoring, extensive daytime sleepiness and apnea that is secondary to partial or complete upper airway collapse (2,3). There is no clear data about the prevalence of simple snoring and upper airway resistance syndrome.

Approximately 2-3 % of children are affected with OSA which may lead to behavioral, cognitive and growth abnormalities (4,5,6). The most common cause of SDB in childhood is upper airway obstruction due to adenotonsillar hypertrophy. Therefore, adenotonsillectomy (AT) is the most commonly used treatment modality for SDB (7). The overall complication rate of AT is in the range of 5% to 34% (7). In addition, the reported rate of residual SDB is more than 20% in children who underwent AT.[7] For these reasons, the current studies are trying to clarify the role of medical treatment for SDB (8,9). Anti-inflammatory agents (corticosteroids, leukotriene receptor antagonists, ketotifene and chromones) are proposed as an effective and non-surgical treatment option for SDB (10).

Topical nasal corticosteroids (TNC) are the most commonly used anti-inflammatory agents for SDB. TNC has been used for a long time as a first line treatment for allergic rhinitis which is associated with chronic nasal obstruction, sleeping disturbance and snoring (11). Recent studies showed that TNC reduces the adenoid tissue volume while improving SDB symptoms (12). The effect mechanisms of TNC are well established in the literature, but the histopathological findings of lymphoid tissue after topical corticosteroid application are still not clear.

In this study of children with SDB, the histopathological changes were analyzed in comparison with a control group of TNC treatment. For this purpose, adenoid tissues were evaluated by light microscopy.

MATERIAL AND METHODS

Study design and patients: This study is designed as a retrospective controlled clinical trial in an academic tertiary referral center between Aug 2013 and April 2015. A total of 752 adenoidektomi case files were reviewed retrospectively and subjects were included in the study if they had a nasophayngeal obstruction more than 70 % in pre-operative flexible endoscopic examination. Subjects were excluded from the study if they met any of the following criteria: 1) tonsillectomy for any reason, 2) craniofacial anomaly or any co-morbidities, 3) active upper airway infection in the past month, 4) history of anti-inflammatory and immunosuppressant medication, 5) otitis media with effusion during surgery. All patients included in the study who used regular TNC pre-operatively for at least 6 weeks (Group A). Group A included 148 cases that fit the inclusion criteria. The most common TNC molecule was mometoson fruoat and we eliminated the other molecules for homogenization. The final study group included 51 patients that fit the inclusion criteria. A control group (Group B) was created randomly from the patients who have no history of TNC preoperatively. Group B included 59 subjects who were all operating were with the same technique (classic curettage addenoidectomy) by the well experienced surgeons.

Evaluations and patient management: All post-operative specimens were reviewed retrospectively at the Department of Pathology. To evaluate the differences in histological findings in children with Group A and Group B the resected tissue of every patient was histologically examined. Specimens were fixed in 10% buffered formalin for 24 hours, and then fixed in paraffin and processed according to routine techniques of light microscopy. Slides 5µm thick were stained with hematoxylin and eosin. Sections were examined with a light microscope (Olympus Bx50) by X400 and X100 (40x and 10x objective lens, 10x ocular lens, 0.151 mm2) magnification. Follicular hyperplasia, chronic inflammation, acute inflammation and goblet cell hyperplasia staining scores were evaluated semi-quantitatively. . The specimens were investigated under light microscopy in a single blind manner and their staining scores were evaluated semi-quantitatively as: 0=none, 1=minimal, 2= moderate, 3=severe. Other parameters such as squamous metaplasia, fibrosis, atrophy, ulceration and hemorrhage were categorized as either present or absent.

Statistical analysis: The statistical analysis was performed with SPSS 16 using the "student test for Equality of means", Pearson "Chi-Square", "Mann-Whitney test", "Wilcoxon W test", appropriately.

RESULTS

There were 51 patients in the Group A and 59 patients in the Group B. The mean age was 7.49 ± 3.24 and 7.53 ± 2.94 in the Group A and Group B, respectively. There were no statistical differences between the groups according to sex and age (Table 1). There was also no statistical difference between groups according to pre-operative adenoid size (Table 1).

Table 1. Patient demographics

	Group (n:51)	Group B (n:59)	p value
Age	7.49 ± 3.23	7.52 ± 2.93	0,95
Sex (Male/Female)	28/23	31/28	0,06
Pre-op tonsil size	2.11 ± 0.71	2.46 ± 0.88	0,08
Pre-op adenoid size	82.74 ± 9.65	78.44 ± 15.95	0,09

The mean scores of follicular hyperplasia (Figure 1) were 2.20 ± 0.75 and 2.58 ± 0.63 in the Group A and Group B, respectively (p=0.005). The mean scores of chronic inflammation were 1.98 ± 0.68 in the Group A and 2.31 ± 0.63 in the Group B (p=0.013). The mean scores of goblet cell hyperplasia were 1.40 ± 0.67 and 1.73 ± 0.71 in the Group A and Group B, retrospectively (p=0.020). The Group A was significantly different from the Group B according to follicular hyperplasia, goblet cell hyperplasia and chronic inflammation. We observed that, these inflammation findings were significantly decreased in the Group A. There were no significant differences between the groups according to acute inflammation findings (p=0.090).

The percentage of squamous cell metaplasia was 90.2% in the Group A and 70.9% in the Group B (p=0.011). The percentage of fibrosis was 66.7% and 25.5% in the Group A and Group B respectively (p=0.001).

The percentage of atrophy was 31.4% in the Group A and 9.1% in the Group B (p=0.004). The percentage of ulcer was 62.7% and 38.2% in the Group A and Group B respectively (p=0.010). The percentage of squamous cell metaplasia, interstitial fibrosis (Figure 2), atrophy and ulcers were significantly increased in Group A. Table 2 summarized the results of histopathological analysis. There was no significant difference between the groups according to hemorrhage findings (p=0.130).

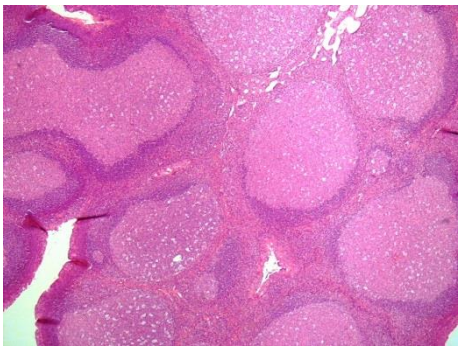

Figure 1. Follicular lymphoid hyperplasia (H&E, X100)

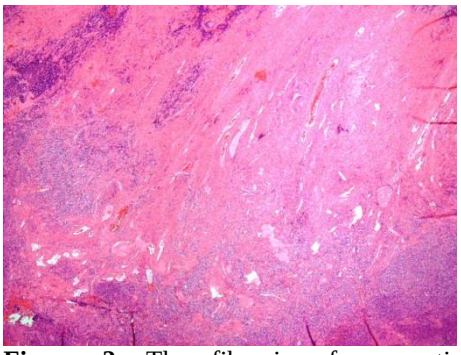

Figure 2. The fibrosis of connective tissue interspersed follicles of adenoid (H&E, X100)

Table 2: Histopathological findings

	Group A (n:51)	Group B (n:59)	p value
Follicular hyperplasia	2.20 ± 0.75	2.58 ± 0.63	**0.005**
Chronic inflammation	1.98 ± 0.68	2.31 ± 0.63	**0.013**
Acute inflammation	1.10 ± 0.30	1.27 ± 0.59	0.090
Goblet cell hyperplasia	1.40 ± 0.67	1.73 ± 0.71	**0.020**
Squamous metaplasia	90.2%	70.9%	**0.011**
Fibrosis	66.7%	25.5%	**0.001**
Atrophy	31.4%	9.1%	**0.004**
Ulcer	62.7%	38.2%	**0.010**
Hemorrhage	70.6%	58.2%	0.130

DISCUSSION

SDB is characterized by intermittent or persistent upper airway collapse during sleep. The airway obstruction is accompanied by snoring, episodic hypoxia/hypercapnia and sleep disturbance (12). This gas exchange abnormalities may trigger the pro-inflammatory cytokines and contribute the upper-airway obstruction secondary to nasophayngeal inflammation (13,14). SDB may lead to numerous morbidities such as neurocognitive disorders, craniofacial growth abnormalities, enuresis and cardiovascular problems if not treated (4,6,13). Adenoidectomy/adenotonsillectomy is the classical treatment option for SDB but it carries a risk of numerous complications (15,16,17).

The recent studies try to clarify the role of medical treatment for SDB, due to a relatively high risk of surgical treatments and persistent symptoms. The anti-inflammatory agents are current research topics in this dilemma. The possible role of chronic inflammation in the nasopharyngeal mucosa encourages the researchers (18,19). Corticosteroids are the most effective anti-inflammatory medications and they are frequently used in the treatment of allergic rhinitis. Systemic corticosteroids are not preferred in the treatment of childhood chronic nasal obstruction because of the side effects (20). TNC is relatively safe and effective treatment for chronic nasopharyngeal obstruction (21-24). The mechanism of TNC is mainly dependent on regulation of local allergic process. It reduces the concentrations of eosinophil and histamine in the nasal secretion as a result of down-regulation T Helper cells (CD3-CD4-CD8), mast cell and Langerhans cells (25,26).

Clinicians are more frequently prescribing TNC for the treatment of childhood SDB. Berlucci et al[21] and Cengel et al[23] have observed the reduced adenoid tissue volume after the TNC treatment. Rezende et al indicate the improved nasal obstruction symptoms after intranasal mometasone furoate treatment which is related with reduced adenoid tissue volume (24). A recently published in-vitro investigation supports an increased apoptotic cell death and decreased pro-inflammatory cytokine produced in a mixed-cell culture system (27). Nevertheless, there is not enough data about the histopathological effects of TNC.

Chronic inflammation process and histopathological findings are variable in cases and severity of chronic inflammation changed between patients. However, severity of inflammation is not always correlated with the severity of SDB. This data supports the multifactorial process of chronic inflammation and SDB. In addition, there is a debate about the role of squamous cell metaplasia in Eustachian tube dysfunction and serous otitis media (SOM) (28-30). The squamous cell metaplasia could be related with chronic inflammation or may be triggered by Eustachian tube dysfunction. Our research team did not involve the cases who have SOM in order to eliminate the possible effects of squamous metaplasia.

We observed a decreased chronic inflammation, follicular hyperplasia and goblet cell hyperplasia after TNC treatment that correlated with the results of Gozal et al[27]. In addition, we observed an increased squamous cell metaplasia, interstitial fibrosis and atrophy in the post-operative specimens. These findings relate with the chronic inflammatory process that has a potential role in pediatric SDB. Suppression of chronic inflammatory process and histopathological effects are proposed as a non-surgical treatment of pediatric SDB. Our findings support the effective role of TNCs in pediatric SDB. The chronic inflammation findings were significantly decreased in the patients who used TNC pre-operatively. In this study, we documented the histopathological effects of TNC.

The main limitation of this article is the lack of physical examination findings prior to TNC treatment. But still, the study group was treated with TNC for chronic nasal obstruction and then underwent surgical treatments due to persistent apnea and lack of complete relief. The second limitation is that we have no histopathological data about the patients who were treated with TNC and completely recovered after the treatment. We did not offer a surgical treatment to these patients and did not analyze the histopathological effects of TNC in children with complete remission.

Conclusion

The TNC in the treatment of SDB is an effective option in light of the current data. However, we are still far away from predicting the good candidates for TNC treatment. We have many patients who do not have any relief with the TNC treatments. It is essential to investigate histopathological and clinical findings in patients who underwent TNC treatment. If we determine good candidates prior to treatment, we can save time and prevent unnecessary medical costs.

REFERENCES

1. Lumeng JC, Chervin RD. Epidemiology of pediatric obstructive sleep apnea. Proc Am Thorac Soc 2008;5(2):242-52.
2. Schlaud M, Urschitz MS, Urschitz-Duprat PM et al. The German study on sleep-disordered breathing in primary school children: epidemiological approach, representativeness of study sample, and preliminary screening results. Pediatr PerinatEpidemiol 2004;18(6):431–440

3. Kaditis AG, Finder J, Alexopoulos EI et al. Sleep-disordered breathing in 3,680 Greek children. Pediatr Pulmonol 2004; 37(6):499–509
4. Chervin RD, Archbold KH, Dillon JE et al. Inattention, hyperactivity, and symptoms of sleep-disordered breathing. Pediatrics 2002;109(3):449-56.
5. Urschitz MS, Guenther A, Eggebrecht E et al. Snoring, intermittent hypoxia and academic performance in primary school children. Am J Respir Crit Care Med 2003;168(4):464-8.
6. Urschitz MS, Eitner S, Guenther A et al. Habitual snoring, intermittent hypoxia, and impaired behavior in primary school children. Pediatrics 2004;114(4):1041-8.
7. Schechter MS; American Academy of Pediatrics, Section on Pediatrics Pulmonology, Subcommittee on Obstructive Sleep Apnea Syndrome. Technical report: diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics 2002;109(4):e69.
8. Alexopoulos EI, Kaditis AG, Kalampouka E et al. Nasal corticosteroids for children with snoring. Pediatr Pulmonol 2004;38(2):161-7.
9. Kheirandish L, Goldbart AD, Gozal D. Intranasal steroids and oral leukotriene modifier therapy in residual sleep-disordered breathing after tonsillectomy and adenoidectomy in children. Pediatrics 2006;117(1):e61-6.
10. Kuhle S, Urschitz MS. Anti-inflammatory medications for obstructive sleep apnea in children (Review) Cochrane Database Syst Rev 2011;(1):CD007074.
11. Bousquet J, Reid J, van-Weel C et al. Allergic rhinitis management pocket reference 2008. Allergy 2008;63(8):990-6.
12. Capdevila OS, Kheirandish-Gozal L, Dayyat E et al. Pediatric obstructive sleep apnea: complications, management, and long-term outcomes. Proc AmThorac Soc 2008;5(2):274-82.
13. Arnaud C, Dematteis M, Pepin JL et al. Obstructive sleep apnea, immuno-inflammation, and atherosclerosis. Semin Immunopathol 2009;31(1):113-25.
14. Unnikrishnan D, Jun J, Polotsky V. Inflammation in sleep apnea: An update. Rev Endocr Metab Disord 2015;16(1):25-34.
15. Bhattacharjee R, Kheirandish-Gozal L, Spruyt K et al. Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: a multicenter retrospective study. Am J Respir Crit Care Med 2010;182(5):676-83.
16. Costa DJ, Mitchell R. Adenotonsillectomy for obstructive sleep apnea in obese children: a meta-analysis. Otolaryngol Head Neck Surg 2009;140(4):455-60.
17. Konstantinopoulou S, Gallagher P, Elden L et al. Complications of adenotonsillectomy for obstructive sleep apnea in school-aged children. Int J Pediatr Otorhinolaryngol 2015;79(2):240-5.
18. Gozal D. Sleep, sleep disorders and inflammation in children. Sleep Med 2009;10 Suppl 1:S12-6.
19. Scadding G. Non-surgical treatment of adenoidal hypertrophy: the role of treating IgE-mediated inflammation. Pediatr Allergy Immunol 2010;21(8):1095-106.
20. Al-Ghamdi SA, Manoukian JJ, Morielli A et al. Do systemic corticosteroids effectively treat obstructive sleep apnea secondary to adenotonsillar hypertrophy? Laryngoscope 1997;107(10):1382-1387
21. Berlucchi M, Valetti L, Parrinello G et al. Long-term follow-up of children undergoing topical intranasal steroid therapy for adenoidal hypertrophy. Int J Pediatr Otorhinolaryngol 2008;72: 1171-1175
22. Demain JG, Goetz DW. Pediatric adenoidal hypertrophy and nasal airway obstruction: reduction with aqueous nasal beclomethasone. Pediatrics 1995;95(3):355-364.
23. Cengel S, Akyol MU. The role of topical nasal steroids in the treatment of children with otitis media with effusion and/or adenoid hypertrophy. Int J Pediatr Otorhinolaryngol 2006;70(4): 639-645.
24. Rezende RM, Silveira F, Barbosa AP et al. Objective reduction in adenoid tissue after mometasone furoate treatment. Int J Pediatr Otorhinolaryngol 2012;76(6):829-31.
25. Andersson M, Andersson P, Pipkorn U. Topical glucocorticosteroids and allergen-induced increase in nasal reactivity: relationship between treatment time and inhibitory effect. J Allergy Clin Immunol 1988;82(6):1019-26
26. Holm AF, Godthelp T, Fokkens WJ et al. Long-term effects of corticosteroid nasal spray on nasal inflammatory cells in patients with perennial allergic rhinitis. Clin Exp Allergy 1999;29(10):1356-66
27. Kheirandish-Gozal L, Serpero LD, Dayyat E et al. . Corticosteroids suppress in vitro tonsillar proliferation in children with obstructive sleep apnoea. Eur Respir J 2009;33(5):1077-84.
28. Kadhim AL, Spilsbury K, Semmens JB et al. Adenoidectomy for middle ear effusion: a study of 50,000 children over 24 years. Laryngoscope 2007;117(3):427-33.
29. Yasan H, Dogru H, Tüz M et al. Otitis media with effusion and histopathologic properties of adenoid tissue. Int J Pediatr Otorhinolaryngol 2003;67(11):1179-83.
30. Eftekharian A, Sabeti S, Khajavi M et al. Light microscopic histopathology of adenoid tissue in otitis media with effusion: is there any relation? Int J Pediatr Otorhinolaryngol 2012;76(11):1598-600.