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


Bulgular: Çalışma grubunda kronik inflamasyon bulguları, foliküler hiperplazisi 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 nasal kortikosteroidler USB'ye nazofaringeal inflamatuar süreci önemli derecede baskı马克 etmektedir. Bu tedavi, en azımdan haif ve orta shıddette USB olan hastalarda cerrahiye alternatif olabilir.

Anahtar Kelimeler: Uykuda Solumum 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 adenoidectomy case files were reviewed retrospectively and subjects were included in the study if they had a nasopharyngeal 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 furoat 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

<table>
<thead>
<tr>
<th></th>
<th>Group A (n:51)</th>
<th>Group B (n:59)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>7.49 ± 3.23</td>
<td>7.52 ± 2.93</td>
<td>0.95</td>
</tr>
<tr>
<td>Sex (Male/Female)</td>
<td>28/23</td>
<td>31/28</td>
<td>0.06</td>
</tr>
<tr>
<td>Pre-op tonsil size</td>
<td>2.11 ± 0.71</td>
<td>2.46 ± 0.88</td>
<td>0.08</td>
</tr>
<tr>
<td>Pre-op adenoid size</td>
<td>82.74 ± 9.65</td>
<td>78.44 ± 15.95</td>
<td>0.09</td>
</tr>
</tbody>
</table>

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).

Table 2: Histopathological findings

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

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)
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 nasopharyngeal 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 al21 and Cengel et al23 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 al27. 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